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Volume 254 JANUARY 5, 1956 Number 1

BIZARRE CLINICAL MANIFESTATIONS OF HYPERTHYROIDISM*

EARLE M. CHAPMAN, M.D.,† AND FARAHE MALOOF, M.D.‡

BOSTON

THE diagnosis of hyperthyroidism is usually easy for the physician. The classic manifestations of the disease are quickly recognized even by those with little clinical experience. Although textbooks refer to masked hyperthyroidism, clinical descriptions of occult forms of the disease are singularly meager. Sattler,[1] an ophthalmologist, recognized and carefully described many of these bizarre forms late in the nineteenth century. We are presenting case histories in some detail for the physician who is interested in following the deceptive preludes, the confirmation of the diagnosis and the response to treatment of patients whose hyperthyroidism was masked or bizarre in its manifestations.

Hyperthyroidism may be established by application of the indexes of thyroid function: the determination of the uptake of radioactive iodine, I^{131}, by the thyroid gland and of the serum protein-bound iodine and the basal metabolic rate. Experience with quantitative in vivo determinations of the retention of I^{131} by the thyroid gland has confirmed the value of the tracer test as a diagnostic tool. External counting over the gland is now done by means of scintillation detectors placed equidistant on a circle with a radius about 40 cm. from the neck of the patient.[2] Measurement is usually made twenty-four to forty-eight hours after the oral administration of a tracer dose of 5 to 20 microcuries of radioactive iodine (hereafter referred to as uptake) and is compared with a standard of an amount of radioactivity equal to that given the patient. Our normal values for the uptake in forty-eight hours are 25 to 55 per cent of the administered dose. Values above 55 per cent are compatible with a diagnosis of hyperthyroidism, and values below 25 per cent are compatible with hypothyroidism; those below 10 per cent are compatible with myxedema. The concentration of protein-bound iodine of the serum is measured by a modification of the method of Chaney.[3] The normal values are 3.5 to 8.0 microgm. per 100 cc. Values above 8 microgm. are compatible with hyperthyroidism and those below 3.5 microgm. are consistent with hypothyroidism or myxedema. The basal metabolic rates are calculated on the basis of the Benedict–Roth standard tables. The normal values are usually considered to be +10 to −10 per cent.

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ABDOMINAL PAIN

CASE 1. P. V. (M. G. H. 577506), a 48-year-old man, entered the Out-Patient Department complaining of an incapacitating steady epigastric pain of 3 weeks' duration. The pain interfered with sleep, and vomiting occurred daily after meals. A physician suspected gall-bladder disease or peptic ulcer, but x-ray studies were normal. An ulcer regimen was advised; however, the patient returned in 9 days with the same pain and was admitted to the hospital with a diagnosis of carcinoma of the pancreas. A variety of diseases were suspected as the cause of his pain. Masked hyperthyroidism was finally considered because of the weight loss, myasthenia, slight stare and pulse rate of 90 on bed rest.

The thyroid gland was firm and twice the normal size. Localized myxedema was present in the lower legs. In the hospital, epigastric pain and vomiting continued. The basal metabolic rates were +21, +17 and +18 per cent. Of a tracer dose of radioactive iodine, 75 per cent was excreted in 48 hours, but this test may have been vitiated by the Graham test performed 24 days previously. Despite exhaustive studies a diagnosis could not be agreed upon. Since a malignant abdominal lesion was suspected, an exploratory laparotomy was performed on July 22, 1947. Careful search of the abdominal cavity revealed no disease. Because of fever and cough after operation, syrup of hydriodic acid, 12 cc. daily, was given for 3 days (equivalent to 700 mg. of iodide daily). After this unintentional test of iodine response the patient was better, and the basal metabolic rates were +5, +6 and +9 per cent.

Further investigation after transfer back to the medical service failed to explain the recurrent epigastric pain. However, with the cessation of the iodide, atrial fibrillation and a rise in the basal metabolic rate to +35 developed, and the diagnosis of hyperthyroidism now seemed likely; he was therefore given a therapeutic trial of potassium iodide. The basal metabolic rate fell to 0 in 10 days, and the abdominal pain ceased. On August 27 a subtotal thyroidectomy was done, and 26 gm. of hyperplastic thyroid tissue was removed. He made an excellent recovery and when he was last examined in August, 1951, the basal metabolic rate was −12 per cent, and he stated that he had had no abdominal pain since 1947.

Abdominal pain as an outstanding complaint in hyperthyroidism was emphasized in 1931 by Verbrycke.[4] Our experience with this manifestation is

dramatically demonstrated by this patient, who had abdominal pain and vomiting as the chief complaint of what proved to be hyperthyroidism. Exploration of the abdomen for suspected carcinoma of the pancreas revealed no disease. Two tests of iodine response were positive. Uptake and serum protein-bound iodine tests were vitiated by a previous Graham test. The diagnosis was proved by the response to iodine and to subtotal thyroidectomy, and the patient has remained free of abdominal pain. We have seen several hyperthyroid patients with abdominal pain simulating gall-bladder or liver disease, peptic ulcer or pancreatitis.

Peripheral Edema

Case 2. A. G. (M. G. H. 737902), a 50-year-old woman, entered the hospital on May 15, 1951, complaining of swelling of the feet and hands of 2 days' duration. Physical

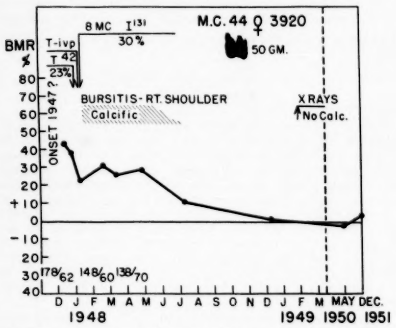

Figure 1. *Course of Coexistent Periarthritis and Hyperthyroidism in Case 4.*
Note the transitory depression of thyroid activity caused by an intravenous pyelogram (ivp).

examination showed marked pitting edema of the ankles, legs, sacrum and hands. The mechanism for the edema was obscure. The thyroid gland was twice the normal size. There was a Grade 3 precordial systolic murmur, without cardiomegaly or signs of increased venous pressure. The lungs were clear, and there was no hepatomegaly.

The pulse was 100 and regular, and the blood pressure 110/70.

X-ray examination of the chest revealed a normal heart outline and no pulmonary congestion. An electrocardiogram was normal, with a regular rhythm, at a rate of 100. Renal and liver-function studies were negative. The venous pressure was 18.0 cm. of saline solution; the circulation time (Decholin, arm-to-tongue method) was 12 seconds.

Because of the thyroid enlargement it was decided to exclude hyperthyroidism. On the basis of serial basal metabolic rates of +36, +37 and +32 per cent, an uptake of 74 per cent and a serum protein-bound iodine of 12.2 microgm. per 100 cc., the diagnosis of hyperthyroidism was established. On June 15 she was treated with 7.0 millicuries of I^{131}, of which she excreted 17 per cent in the urine in 48 hours. Within 1 month of this treatment she was euthyroid, and the edema had disappeared.

Peripheral edema as a presenting complaint of hyperthyroidism has been seen in several patients. The mechanism is obscure; heart disease, renal disease, nutritional deficiency, abnormal serum protein, liver disease and obstructive phenomena were all absent. The edema disappeared when the hyperthyroidism was controlled.

Heart Failure

Case 3. J. T. (M. G. H. 786679), a 69-year-old man, was admitted to the hospital on August 29, 1952, because of swelling of the genitalia of 2 weeks' duration. He was ill and confused; it was learned that he had been dyspneic for 4 years and that he had noted weight loss and weakness for a few months.

Physical examination disclosed poor nutrition and icteric scleras, with evidence of congestive heart failure, including dilated neck veins, hydrothorax, an enlarged heart, atrial fibrillation with a rapid ventricular rate and a loud, blowing, Grade 3 apical systolic murmur. The abdomen was distended, and the liver was enlarged. There was edema of the anterior abdominal wall, scrotum, penis and legs. The diagnoses were chronic congestive heart failure and probable cirrhosis of the liver.

Under treatment with diuretics and digitalis, the edema and other signs of congestion disappeared, but atrial fibrillation persisted, the ventricular rate varying from 70 to 85 per minute.

After 10 days in the hospital the suspicion deepened that some chronic wasting disease was present. Although a goiter could not be felt, it was decided to exclude hyperthyroidism because the circulation time was found to be rapid. An uptake on September 11 was 98 per cent; the serum protein-bound iodine was 14.4 microgm. per 100 cc., and the basal metabolic rate was + 37 per cent. The diagnosis of hyperthyroidism was confirmed by these indexes of function, and consequently, on September 25, the patient was treated with 8.8 millicuries of I^{131}. In the following months he responded to the radioactive iodine, and in July, 1953, the indexes of thyroid function were normal.

This case illustrates the importance of the indexes of thyroid function in elderly patients with the signs of heart failure and disorders of cardiac rhythm. The diagnosis of hyperthyroidism was unsuspected during the first week in the hospital. One reason then advanced against this diagnosis was the adequate response of the cardiac rate to digitalis, which is at variance with classic teaching. However, this response of the ventricular rate to the usual dose of digitalis in patients with hyperthyroidism has been observed by us in a number of patients, especially those who are elderly and debilitated.

Periarthritis of the Shoulder

Case 4. M.C. (M.G.H. 602063), a 44-year-old woman with hyperthyroidism, made an excellent response to radioactive iodine, with concomitant clearing of subacromial bursitis and disappearance of calcification (Figure 1). The transitory depression of thyroid avidity for I^{131} caused by an intravenous pyelogram is also shown in this figure. Three days after the pyelogram she excreted 19 per cent more of the tracer than the previous one, but 4 days later she excreted only 7 per cent more of a therapeutic dose. This indicates that the pyelogram affects the avidity of the hyperplastic thyroid gland for only a short interval. We have found that in most cases the excretion of radioactivity from a tracer and a therapeutic dose in the same patient check within 5 per cent.

Subacromial bursitis has been coexistent in about 4 per cent of our patients with hyperthyroidism. Meulengracht and Schwartz[5] found that 27 per cent

of patients with tendonitis or bursitis of the shoulder had some form of thyroid disease. Recently, Skillern[6] revived interest in this association of diseases. In his experience periarthritis was resistant to all forms of therapy until the hyperthyroidism was controlled. Orthopedic surgeons, who usually treat these patients, should be alert to the possible role of the thyroid gland in diseases of the shoulder.

Osteoporosis

Case 5. W.F.M. (M.G.H. 25200), a 45-year-old man, fell and forcibly hyperextended the right arm in 1942. Subsequently, he had weakness, pain and wasting of the right hand and arm, was unable to continue work and had only osteopathic treatment. By 1945, weakness of grip and muscle wasting had disappeared. However, pain and disability continued, and he consulted several physicians without benefit. He entered the Baker Memorial Hospital in January, 1947, when Lhermitte's syndrome of post-traumatic demyelinization of the cervical cord was considered, but thorough neurologic investigation failed to support such a diagnosis. Likewise, there was no evidence of a ruptured cervical disk.

In November, 1949, the patient re-entered the hospital because of pain in the upper back, weakness of the legs and numbness of the hands and feet of 3 weeks' duration. He was hoarse and had difficulty swallowing solid food. In addition, he still had the pain in the right arm. The weakness progressed in a few days to the point where walking was almost impossible. The spinal fluid was clear, without cells and with a total protein of 166 mg. per 100 cc. The serum calcium was 8.6 mg., and the phosphorus 3 mg. per 100 cc., and the alkaline phosphatase 3.2 Bodansky units. Urinary calcium excretion was persistently elevated. Roentgenograms showed considerable bone atrophy of the thoracic and lumbosacral spine.

In the 6 weeks in the hospital he improved gradually. The bone atrophy and the hypercalcuria were unexplained. A diagnosis of acute multiple neuritis and osteoporosis was made, and he was treated with a low-calcium diet and methyltestosterone.

In December, 1950, he re-entered the hospital because of painful, moist feet with burning, paresthesias, and nervousness. The spinal fluid was normal. The thyroid isthmus was palpable, and low-grade hyperthyroidism was mentioned as a possible cause of the severe osteoporosis; a single basal metabolic rate was +14 per cent.

In May, 1952, when seen in the Neurological Clinic, he again complained of paresthesia in the fingers, "shaking hands" and fatigue. The thyroid gland was diffusely enlarged,—to at least three times the normal size,—and he was referred to the Thyroid Clinic. The uptake was 52 per cent, and the serum protein-bound iodine was 12.0 microgm. per 100 cc. This evidence established the diagnosis of hyperthyroidism, and so, on May 29, he was treated with 10 millicuries of I^{131} and excreted 41 per cent of this dose in the following 48 hours. By August, he was amazingly better, had gained 5 kg. in weight and was able to work all day. On October 14 the basal metabolic rate was +2 per cent. Roentgenograms showed the same degree of demineralization.

On December 23, 1952, the basal metabolic rate was +16 per cent, the uptake 28 per cent, and the serum protein-bound iodine 5.7 microgm. per 100 cc. He seemed well and was working regularly. On November 17, 1953, the basal metabolic rate was +15 per cent, the uptake 40 per cent, and the serum protein-bound iodine 5.8 microgm. per 100 cc. Roentgenograms of his lumbar spine, pelvis and skull showed a questionable decrease in the degree of demineralization in comparison with the films taken in October, 1952. However, this slight difference could be attributed to variability in radiographic technic. This type of demineralization is seldom a reversible process, but so far, in this patient, there is probable roentgenographic evidence of a return of the bone structure toward normal. In June, 1954, the indexes of thyroid function were normal, and the urine excretion of calcium was 39 mg. in 24 hours.

Excessive loss of calcium and phosphorus in the urine and stool is an established fact in patients with hyperthyroidism; this may result in demineralization.[7] Indeed, the demineralization may be severe, and fracture, with failure of the bone to heal, may be a presenting sign of hyperthyroidism.[8]

Severe Myopathy

Case 6. S.G. (M.G.H. 295933), a 38-year-old woman, entered the Out-Patient Department in April, 1941, complaining of pain in the right shoulder and arm, nervousness, hoarseness and a nasal discharge. Despite frequent visits and a variety of treatments, she did not improve. In October she entered the Emergency Ward because of difficulty in breathing and a crowing sound on respiration. Examination revealed little except failure of the vocal cords to abduct. Consequently, on October 7, a tracheotomy was done although a psychiatric consultant had suspected hysteria and advised conservative treatment. At operation a large pyramidal lobe of the thyroid gland was encountered and removed; the pathological diagnosis was involution.

Through the years she continued to have numerous complaints and often visited the Out-Patient Department concerning her tracheotomy tube. On March 21, 1951, a Lynch suspension and intralaryngeal left-sided arytenoidectomy was done. This improved the airway, but the patient behaved strangely. She had severe anxiety, remained in bed and refused the operation on the right arytenoid cartilage. The pulse rate was rapid during bed rest. In June, 1951, she re-entered the Eye and Ear Infirmary because of weakness and shortness of breath. A medical consultant made the diagnosis of congestive heart failure and transferred her to the Medical Service. On June 11 the visiting physician, Dr. Charles H. Du Toit, suspected hyperthyroidism. Because of her tracheotomy, the basal metabolic rate could not be determined, but the serum protein-bound iodine was found to be 14 microgm. per 100 cc. and the uptake to be 74 per cent. When seen on June 20 she was lying in a flaccid state, jerking occasionally and coughing frequently and saying with difficulty that she had been weak in the muscles for over 10 years. The goiter was estimated to be 3 times the size of the normal thyroid gland. On June 21 she was treated with 9 millicuries of I^{131}.

By August 28 she was much stronger and was doing some housework. The serum protein-bound iodine was 4.0 microgm. per 100 cc. By October 23 she was clinically hypothyroid; the uptake was 2.0 per cent. Consequently, she was given thyroid, 60 mg. daily. The tracheotomy tube was removed, and she breathed very well, but the opening closed so slowly that on February 4, 1952, an operative closure of the wound was done. On December 2, 1953, the basal metabolic rate was −13 per cent and she seemed very well, taking thyroid, 60 mg. daily; the serum protein-bound iodine was 6.7 microgm. per 100 cc.

A unique experience was encountered in the patient just discussed. Reconstruction of the probable sequence of events makes it seem likely that she was hyperthyroid for ten years and that the abductor paralysis of the vocal cords for which a tracheotomy was done in 1941 was, in fact, caused by myasthenia of the vocal cords due to hyperthyroidism.

The myopathy of hyperthyroidism may create such muscle weakness that the patient has difficulty in walking. Two patients with myopathy were confined to wheel chairs until after their response to radioactive iodine. The onset of myasthenia may be so rapid as to simulate "periodic paralysis." Sattler[1] says that such patients are momentarily unable to

walk because of a buckling of the legs, and they have been known to fall without having any feeling of dizziness. The reflexes are reduced or entirely absent. The myasthenia of hyperthyroidism does not respond to neostigmine. Often, the voice is weak, and the speech may be nasal in quality. The tremor consequent to the disease was suspected of being associated with degenerative nervous disease in 2 patients from this clinic and of being hereditary in a third. In all cases the tremor disappeared after control of the hyperthyroidism with radioactive iodine. In 1 patient with Parkinson's disease and hyperthyroidism the tremor decreased greatly after therapy.*

Encephalopathic Form of Hyperthyroidism

Case 7. J.C. (M.G.H. 589799), a 62-year-old French-Canadian woman, entered the hospital on September 9, 1947, with a chief complaint of diarrhea. Since 1941, after 2 sons were wounded in the war, she had noticed nervousness, a slight tremor, anorexia, weakness and a weight loss of 13.6 kg. (30 pounds).

On examination she appeared older than her stated age, and had a stare, tremor of the whole body and marked weakness of all musculature. The thyroid gland was not palpable. The pulse was 120 and regular. The basal metabolic rate was +74 per cent. The serum protein-bound iodine was 18.6 microgm. per 100 cc., and only 7.0 per cent of a tracer dose of I^{131} appeared in the urine in 48 hours.†

One week later she became greatly disturbed after insertion of a catheter in the bladder. The pulse rate was rapid, and pulmonary congestion developed. This attack was then interpreted as acute failure of the left ventricle. Accordingly, she was treated with oxygen by nasal catheter, tourniquets, Cedilanid, 1.2 mg. intravenously, and morphine, 10 gm. She was wildly disoriented, and her speech became incoherent. Later, it was disclosed that 2 weeks previously she had had a similar episode at home, but this had cleared in a few hours. Twelve hours after this disturbance she was quieter; the temperature was 100°F. by rectum, the pulse 140 and regular, and the lungs were clear.

She remained in the same state, with aphasia, grimacing, restless, whining and responding only with "yes" to any questions. The reflexes were all diminished or absent. A thyroid crisis was considered, but Dr. B. Skanse suspected that she might have the encephalopathic form of hyperthyroidism, a clinical pattern with which we were not then familiar. Propylthiouracil, 500 mg. daily, was started. Three days later she was smiling and saying a few words, and could sit up and hold out her hands. On the next day improvement was dramatic. She took an interest in her food, her surroundings and her personal toilet; she became alert and responsive, and on the following day said that she would "be well in a week or 2." A goiter was palpable for the 1st time deep on each side of the neck. The basal metabolic rate was now +99 per cent, and the serum protein-bound iodine was 13 microgm. per 100 cc.

Propylthiouracil was discontinued on September 28, and on October 5 she was treated with 10 millicuries of I^{131} and excreted 6 per cent in the urine in the following 48 hours. On October 9 the basal metabolic rate was +71 per cent. She was walking in the corridor and happy to go home on October 12. The pulse rate was 100 per minute.

On October 24 she died suddenly at home after a sharp attack of precordial pain that came on while she stood on a ladder hanging curtains. Autopsy (M.G.H. 12643) revealed a recent myocardial infarction and thyroid hyperplasia. There were no gross changes in the brain, but microscopical examination disclosed slight to moderate swelling of oligodendroglia in the subcortical white matter. The medulla and midbrain were normal. These findings could not be explained by circulatory changes secondary to the recent myocardial infarction, but might have been a residuum of the stupor during her hospital stay, according to Dr. Charles S. Kubik, neuropathologist.

Case 8. M.W. (M.G.H. 745330), a 67-year-old Polish woman, had been well until 1945, when the diagnosis of hyperthyroidism had been made while she was in a hospital in New York City for a cholecystotomy. Lugol's solution was prescribed, but was taken for only 1 month. Thereafter, she was well until 1950, when she had pneumonia, congestive heart failure and atrial fibrillation. She was treated with digitalis, mercurial diuretics and a low-sodium diet. Hyperthyroidism had recurred, and so propylthiouracil was advised. This program was continued until the middle of 1951, when the antithyroid drug was stopped because of a depression of the leukocytes.

When the symptoms and signs of hyperthyroidism returned in June, 1952, she was given Itrumil (iodinated antithyroid), but when she failed to respond she was again given propylthiouracil. She did not improve, and in November the propylthiouracil was increased to 400 mg. daily. She lost weight rapidly, became short of breath, had diarrhea and found it difficult to move her legs. A marked tremor and a scaling dermatitis appeared.

On admission to the Massachusetts General Hospital on December 17, 1952, she was emaciated, tremulous and constantly active, and had a lobular goiter that was at least 5 or 6 times the size of the normal thyroid gland. The heart was enlarged, and atrial fibrillation was present. There was bilateral edema of the ankles. The blood pressure was 190/50. The eye signs were minimal. On December 22 the basal metabolic rate was +51 per cent, and the uptake 90 per cent. A roentgenogram of the chest showed marked deviation of the trachea and esophagus by the goiter.

A lively discussion of the best way to treat the hyperthyroidism ensued. She became disoriented, delirious and unable to communicate. The diarrhea was worse. Profound muscle weakness confined her to bed. The final decision was to treat her with radioactive iodine and, after she improved, to do a subtotal thyroidectomy. It was thought that the deviation of the mediastinal structures would not be relieved by radioiodine treatment alone (Fig. 2). On December 24 she was held upright in bed while she swallowed 22.8 millicuries of I^{131}. Because of the urgency of her illness it was suggested that this be followed with an antithyroid drug in the hope of shortening the interval of response. Tapazole (1 methyl-2-mercaptoimidazole), 15 mg. every 6 hours, was started on January 1, 1953. Two days later the goiter was tender, and she had signs of radiation thyroiditis that lasted several days. She remained in a precarious state, with diarrhea, disorientation, and profound weakness. The weight declined steadily, from 59.9 kg. (132 pounds) on entry to 50.3 kg. (111 pounds). She vomited food and medication. By January 19 the pulse was 94, but atrial fibrillation and diarrhea persisted. The mental confusion diminished gradually. On January 28 she was discharged, to continue Tapazole, 10 mg. every 8 hours, and digitoxin, 0.1 mg. daily.

One month later she returned to the clinic in much better health, having gained 5 kg. (12 pounds). The diarrhea and mental confusion had disappeared. She continued Tapazole, 10 mg. twice daily, until April 17, 1953. On April 21 the basal metabolic rate was +18 per cent. A remarkable change was apparent. She was active at home and had regained full interest in her surroundings. The serum protein-bound iodine was 5.2 microgm. per 100 cc. To assay the response to I^{131} the Tapazole was stopped, and 4 days later the uptake was 78 per cent. By May 26 the basal metabolic rate was +45 per cent, and symptoms of hyperthyroidism were returning. On May 26 she was given a 2d therapeutic dose of 15 millicuries of I^{131}, of which she excreted only 10 per cent in the urine in 48 hours.

She failed to make a complete response to the 2d dose, and since the uptake was found to be 68 per cent she was

*It was this experience that led to an investigation of the value of radioiodine therapy in euthyroid persons with Parkinson's disease.9

†100 minus this value gives the presumed percentage of I^{131} retained by the thyroid gland.

given a 3d dose of 15 millicuries of I^{131} on December 31, 1953. On February 9, 1954, the basal metabolic rate was +14 per cent, and she was judged to be euthyroid. On August 17, 1954, comparative roentgenograms showed that the displacement of the esophagus and trachea was no longer present (Fig. 2).

Manifestations of neurologic disease that have overshadowed the usual symptoms and signs constitute another bizarre clinical form of hyper-

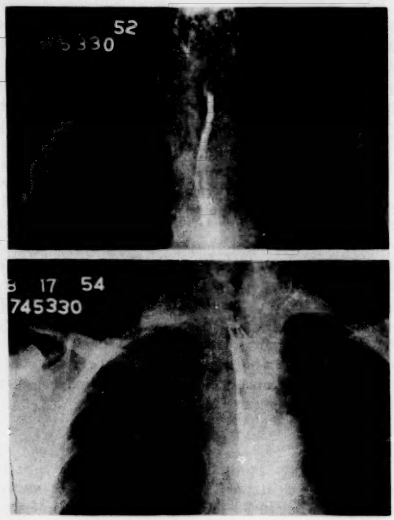

FIGURE 2. *Roentgenograms in Case 8, Showing the Return to Normal Position of an Esophagus Displaced by a Substernal Toxic Goiter Treated with Radioactive Iodine.*

thyroidism. Waldenström[10] called attention to these manifestations and described 10 patients with hyperthyroidism seen between 1935 and 1945 who suffered hemiparesis or bulbar paralysis with inability to swallow. This he called the encephalopathic form of hyperthyroidism. In 3 of his patients no lesions in the brain were found at autopsy. Since our patients improved after I^{131} without the addition of stable iodine, the old theory of iodine deficiency as the cause of such encephalopathic symptoms[10] seems disproved.

EPILEPSY

CASE 9. C.P. (5243),* a 24-year-old woman, was well until August, 1951, when she had a convulsion that lasted for 20 minutes. She was taken to the Boston City Hospital, where the diagnosis of hyperthyroidism was established and treatment with 300 mg. of propylthiouracil daily was begun. She took this regularly until February 3, 1952, when the dose was reduced to 150 mg. daily. In spite of this therapy, she continued to be tired and nervous and to have headaches, for which she was taking 2.69 gm. (40 gr.) of aspirin daily. When she was first seen on February 27 the thyroid gland was 3 times the normal size and she seemed toxic despite normal basal metabolic rates; all treatment was stopped. Four days later an electroencephalogram was abnormal, without localization. The predominant rhythm was 10-per-second alpha waves with 30-per-second beta waves. Diffuse 4-per-second to 6-per-second waves appeared in all leads, but they arose more frequently and were of greater amplitude in the midline. Hyperventilation was accompanied in the 1st minute by the appearance of paroxysmal bursts of 4-per-second to 5-per-second activity of 200 microvolts.

On March 21 she was treated with 7 millicuries of I^{131}, of which 17 per cent was excreted in the urine in the following 48 hours.

By June, 1952, the patient had declined into hypothyroidism. The basal metabolic rate was −24 per cent, and the serum protein-bound iodine was 2.5 microgm. per 100 cc. Thyroid, 60 mg. daily, was advised. In February, 1953, she was advised to increase thyroid to 120 mg. daily, but during the summer she stopped all treatment. In October the indexes of thyroid function were normal, and she reported having no more headaches or seizures. She appeared euthyroid, and an electroencephalogram was within normal limits when compared with previous tracings.

In this case the onset of hyperthyroidism was manifested by a convulsive seizure. The electroencephalogram before treatment was abnormal and much like that seen in epilepsy. After the patient responded to radioactive-iodine therapy for hyperthyroidism the electroencephalogram was normal. Condon, Becka and Gibbs[11] recently reported on the electroencephalographic abnormalities in hyperthyroidism but stated, "it is noteworthy that in spite of the great number of definite spike discharges in 7 cases, no clinical seizure occurred."

*Private patient of one of us (E.M.C.).

SUMMARY

Bizarre manifestations of hyperthyroidism, including abdominal pain, peripheral edema, heart failure with an adequate response of the cardiac rate to digitalis, periarthritis of the shoulder, skeletal demineralization, severe myopathy, encephalopathy and epilepsy, are discussed. It is hoped that this presentation will alert physicians to the recognition of curable disease that may mimic disease for which the patient may otherwise receive ineffective therapy.

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PERSISTENCE OF ANTITOXIN LEVELS AFTER TETANUS-TOXOID INOCULATION IN ADULTS, AND EFFECT OF A BOOSTER DOSE AFTER VARIOUS INTERVALS*

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ALTHOUGH various previous observations, chiefly by French, American and Canadian investigators, had indicated that tetanus toxoid immunization was a powerful tool in the prevention of tetanus, it was not until the experience of the United States and British armed forces in World War II that the truly remarkable effectiveness of this product was made clear. The American record was particularly impressive, only 14 cases of tetanus occurring in the United States Army and Navy during the war.[1,2] The two services established basic immunity with 3 doses of fluid toxoid (Army) or two doses of alum-precipitated toxoid (Navy), a booster dose at one year and subsequent booster doses either before departure for a combat theater (Army) or at four-year intervals (Navy). In addition both services administered an emergency booster dose as soon as possible after wounding or other injury of the type ordinarily incurring the risk of tetanus.

In 1949 the United States Army, Navy and Air Force jointly adopted the procedure of administering two doses of precipitated tetanus toxoid one month apart, a third dose approximately one year later and booster doses every four years and after injury. A similar procedure has been widely used in civilian practice since World War II. However, two important questions remained unsettled: What was the duration of immunity after active immunization with tetanus toxoid? And how many years after the last previous dose of toxoid would a subject respond satisfactorily to a booster inoculation? The practical significance of these questions was brought to a head by the frequent necessity of considering the use of toxoid in civilians formerly in the armed forces, and in the return to active duty of men who had served some years previously during World War II. Furthermore, the scanty suggestive evidence reported by Long and Sartwell[1] and by Baird[3] indicated that the interval between routine booster inoculations might perhaps be safely extended beyond four years, with a consequent reduction in the ultimate number of inoculations required. On the other hand Miller, Ryan and Beard[4] reported in 1949 that, at intervals of four years or more after the last previous toxoid, the response elicited by an alum-precipitated booster was definitely slower than it was with a shorter interval.

A preliminary study in medical students in 1949-50 indicated that fairly good levels of antitoxin were maintained for as long as six years after the last booster dose received during military service, and that the postbooster response yielded titers generally in excess of 10 units per milliliter by three weeks after inoculation. A larger and more extended study was therefore undertaken in veterans employed by the Veterans Administration. The results of the combined studies are presented below, together with comments on the significance of these and similar studies reported during recent years.

PROCEDURE

Two separate groups were studied. They have been combined in the tabulations. The first study was carried out in 38 second-year medical students, all veterans of World War II, at Boston University School of Medicine. These subjects had gone one to six years since their last tetanus-toxoid injection. Each student was bled for antitoxin determination and then injected subcutaneously with 0.5 cc. of fluid tetanus toxoid containing 1 Lf of diphtheria toxoid.‖ Three weeks later another bleeding was taken.

The second group consisted of 106 World War II veterans employed at the Boston Regional Offices of the Veterans Administration who had gone four to ten years since their last injection of toxoid. Each subject was bled, injected with 0.5 ml. of standard Army-issue alum-precipitated tetanus toxoid, and bled again at six and fourteen days. Sixty-eight of the 106 subjects were bled again at the end of a year. A few samples from the first and second bleedings, and a majority of the samples from the third bleeding, were not available for titration because of technical difficulties in storage, handling or shipping of the specimens.

Titrations were performed by intramuscular injection of mice with appropriate dilutions of the

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serum under test, mixed with a standardized dose of test toxin at a tenth or a hundredth of a test-dose level, depending on the level of antitoxin sought. Serum samples were tested from the level of 0.025 antitoxin unit per milliliter (hereafter designated "u./ml." or "units") upward at threefold intervals for the prebooster and twenty-one-day bleedings, and at twofold intervals for the six-day, fourteen-day and one-year samples. The values given in the test and used for purposes of calculation are the geometric means between the highest concentration of each serum sample at which symptoms of tetanus appeared, and the next higher concentration tested.* Controls with standard antitoxin from the National Institutes of Health were included regularly. The number of mice used per specimen ranged from 7 to 11.

Both in the presentation and in the discussion of the data of this study, some attention will be given to the number of serum specimens via each group that showed titers above or below ± 0.1 u./ml., the level most commonly regarded as representing the threshold of the "protective level." The significance of such a "protective level" and the status of the evidence for its selection will be dealt with in the discussion.

Results

Prebooster Antitoxin Levels

Table 1 gives the distribution of prebooster antitoxin titers found, in accordance with the interval since the last dose of toxoid. It is seen that 35 out of 144 persons (24 per cent) had titers below 0.08 u./ml. whereas 14 (9.7 per cent) had titers below 0.025 u./ml., some or all of which may have been less than 0.01 u./ml. The table gives the impression that the average level at nine and ten years after the last dose of toxoid is definitely lower than at shorter intervals. However, because of the small numbers the difference noted is not statistically significant.

*Exact geometric means were employed in the calculations (except for the interpolation required in the handling of the lowest and highest titers observed). Data cited in the text, however, are rounded off to the nearest significant figures.

Postbooster Antitoxin Levels

Table 2 shows antitoxin levels before and after booster inoculations, in relation to the interval since the last injection of toxoid. To simplify comparison and statistical analysis, year groups have been combined into groups of roughly comparable size.

TABLE 1. *Antitoxin Level before Booster Dose.*

Interval Since Last Immunization	Titers (actual ranges tested)							Totals	
	<0.025	>0.025 <0.08	>0.08 <0.25	>0.25 <0.8	>0.8 <2.5	>2.5 <8.0	>8.0 <25.0		
	(geometric means of above)								
	<0.025	0.045	0.14	0.45	1.4	4.5	14.0	Number	Geometric mean
yr.									unit/ml.
10		1	1	1				3	0.14
9		3	2	2				7	0.12
8	2	3	5	3	4	8	1	26	0.59
7	3	4	12	13	3	4	2	41	0.32
6	4	3	4	3	4	4		22	0.25
5	3	1	1	5		3		13	0.26
4	1	4	2	1	2	2		12	0.24
3		1	2	3		1	1	8	0.51
2	1		1		1	1		4	0.36
1		1	2	2		3		8	0.60
Totals	14	21	32	33	14	26	4	144	0.34

The average rises observed are fairly characteristic for such observations. The six-day titers show a rise of fivefold to sevenfold above the preinoculation titers, and the fourteen-day and twenty-one-day bleedings show average levels ranging from forty to a hundred times the preinoculation levels. At one year the titers had subsided to levels within a narrow range, the average values being four or five times those observed before inoculation.

Relation between Prebooster and Postbooster Levels

Table 3 and Figure 1 show the average postinoculation levels reached at each time of observation, grouped in accordance with prebooster levels. It is seen that, in subjects having relatively low initial levels, the average postbooster titers did not rise to such high levels as were found in subjects starting with higher preinoculation titers. However, the differences in average postinoculation levels at all times of measurement were relatively slight in comparison to the preinoculation levels. This finding, of course, is not unexpected. Similar studies of the response in

man to diphtheria toxoid[5,6] have shown that the greatest *relative* increase in antitoxin titer after a booster injection of toxoid generally occurred in subjects with the lowest measurable preinoculation titers. Comparable observations have, of course, been made regarding the response to many other antigens.

TABLE 2. *Relation of Prebooster Titers to Postbooster Titers by Interval since Last Toxoid.*

Interval since Last Toxoid	No. in Group	Before Inoculation		After Inoculation	
		Mean Titer	Range*	Mean Titer	Range*
yr.					
6 days after booster (102 specimens):					
8-10	33	0.39	0.28 - 0.54	1.9	1.3 - 2.8
7	40	0.35	0.25 - 0.45	2.3	1.8 - 2.9
4-6	29	0.27	0.19 - 0.38	1.85	1.3 - 2.7
14 days after booster (38 specimens):					
8-10	9	0.66	0.33 - 1.32	25.0	18.5 - 34.0
7	17	0.3	0.21 - 0.42	15.0	12.0 - 19.0
4-6	12	0.31	0.18 - 0.53	11.0	6.5 - 19.0
21 days after booster (38 specimens):					
4-6	18	0.27	0.16 - 0.46	26.0	22.0 - 31.0
1-3	20	0.48	0.32 - 0.72	29.0	24.0 - 35.0
1 yr. after booster (68 specimens):					
8-10	27	0.38	0.25 - 0.55	1.5	1.2 - 1.9
7	25	0.41	0.29 - 0.57	1.9	1.5 - 2.5
4-6	16	0.32	0.20 - 0.51	1.4	1.0 - 1.8

*Within 1 standard deviation.

Adequacy of Response

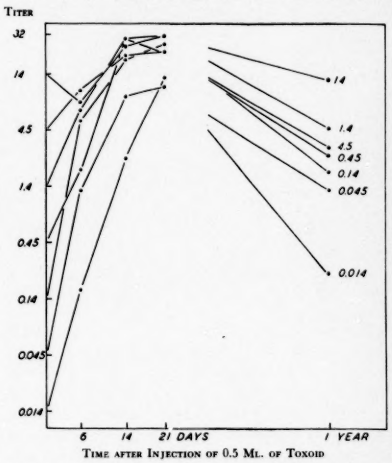
The average postbooster levels found are shown in Table 2. So far as individual responses are concerned, postinoculation bleedings obtained on 7 subjects were not sufficient to establish clearly the nature of the response obtained. Seven others, all with titers between 1.5 and 15 units before boosting, appeared to show some decrease in titer after inoculation. These findings cannot be interpreted, however, as actual decreases since the wide spacing between points of measurement precluded the detection of minor changes in titer. Of the remaining 130 subjects, only 1 (subject 88, discussed below) failed to show a clear-cut response to the booster injection.

TABLE 3. *Relation of Prebooster to Postbooster Titers.*

Prebooster Titer	Average Postbooster Titer							
	6 days		14 days		21 days		1 yr.	
	No.	*Geometric Mean*	*No.*	*Geometric Mean*	*No.*	*Geometric Mean*	*No.*	*Geometric Mean*
<0.025	9	0.12	3	2.3	4	13.0	4	0.17
0.045	14	0.9	4	10.7	7	12.4	9	0.95
0.14	24	3.8	8	13.9	7	47.0	19	1.36
0.45	25	1.4	10	23.7	7	33.0	14	1.9
1.4	12	4.7	5	23.7	2	(55.0)	9	3.3
4.5	15	7.1	7	13.4	10	31.0	10	3.2
14.0	3	5.6	1	(18.0)	1	(55.0)	3	8.8
Totals	102		38		38		68	
Averages		2.0		15.1		28.0		1.5

Findings at each time of postinoculation sampling were as follows:

Six days. The mean titers of all groups bled at six days after inoculation were well above even the most conservative interpretation of a "protective level." However, 4 of the 102 subjects bled at this time exhibited less than 0.1 u./ml. The data for these subjects (subjects 89, 108, 88 and 67) are given in Table 4.



TIME AFTER INJECTION OF 0.5 ML. OF TOXOID

FIGURE 1. *Tetanus-Antitoxin Levels after One Booster Injection, by Groups with Same Initial Level.*

The outcome in subject 89 (1 of the 7 "indeterminate" subjects noted above) is unknown. The response in subject 88 is clearly inadequate; but the one-year levels in subjects 108 and 67 are so nearly comparable with numerous other subjects exhibiting excellent peak responses that they may be assumed to have acquired satisfactory long-term immunity from the booster injection even though their immediate postbooster response was apparently delayed. On the other hand, subject 88 illustrates the fact that there are occasional persons whose antibody response to a booster dose of toxoid is inadequate.

Fourteen to twenty-one days. Of the subjects whose titers were measured at fourteen or twenty-

one days, only 2 showed poor responses. One was subject 88, noted above. In the other, subject 41, the titer rose to 0.55 unit at six and was 0.28 unit at fourteen days (this subject was not seen at one year). The response in the remaining 74 subjects was excellent; only 2 (subjects 39 and 94) failed to exceed 5 units at this peak time of measurement. Subject 39, when seen at one year, still carried 0.3 units, a not uncommon level at the one-year interval.

One year. As with the earlier titers the levels found at one year covered a wide range, from <0.025 u./ml. (subject 88) to 20 u./ml. (subject 16). The one-year titer did not necessarily bear any consistent relation to the six-day or fourteen-day titer, and it bore no relation to the interval since the last previous injection. The 20-unit value at one year was in a subject whose six-day titer was 5.0 although his fourteen-day titer was 1 of the 2 highest observed — >50 <100 units. For comparison, the only other subject with a similar high peak titer at fourteen days (subject 33) ended the year with 2.5 units; 5 other subjects with the highest six-day levels seen (subjects 75, 73, 68, 22 and 63) ended the year with less circulating antitoxin than subject 16. Many other examples of the variability and unpredictability of the response to a tetanus-toxoid booster over a one-year period could be cited from the observations made in this study. Thus, although the average trend at one year showed a consistent relation to the average titers observed at each previous time of measurement (Fig. 1), wide deviations from this pattern appeared in individual subjects.

If 0.1 u./ml. is accepted as an "adequate" level at one year after a booster, only 1 (subject 88) of the 68 tested at this time failed to maintain an adequate level. Nine additional subjects who had 0.3 unit at one year and 1 (subject 76) who had 0.15 unit might be regarded as having doubtful protection for the ensuing several years before their next probable routine booster. However, Wishart and Jackson,[7] who followed a similar number of subjects for *three* years, found that the major drop in titer occurred in the first year. The number of subjects in their study group who had less than 1 unit when bled were as follows: at four weeks, 1 of 57; at one year, 9 of 58; at two years, 13 of 52; at 3 years, 12 of 51.

Thus, it appears that out of the 68 subjects submitted to long-term study in our group, the prospects for long-term immunity were good in 66 and doubtful in 1 (subject 76); only subject 88 represented an immunologic failure.

Discussion

Bigler,[8] in a ten-year study of the responses of about 300 children to tetanus toxoid, found that all subjects receiving three or more injections of (mostly alum-precipitated toxoid) sustained titers greater than 0.1 u./ml. for at least six months, and after four or more injections this level was sustained for two years or longer. Subsequently, a small but increasing proportion of subjects fell below this level. At five years or more, two thirds to three fourths of the subjects in every group except "3 injections plus booster" had fallen below this level (in that group only 7 subjects were so classified, 3 of whom had titers below 0.1 u./ml.). Sachs[9] found less than 0.1 unit in 3 of 20

Table 4. *Antitoxin Levels of Subjects Discussed in the Text.**

Subject	Interval since Last Toxoid	Pre-booster Titer	Postbooster Titer		
			at 6 days	at 14 days	at 1 yr.
	yr.				
89	8	<0.025	<0.025	—	—
108	8	<0.025	<0.025	—	0.3
88	6	<0.025	<0.025	<0.2	<0.025
67	5	<0.025	<0.025	—	0.6
41	6	0.05	0.6	0.3	—
94	7	<0.025	0.6	2.5	—
39	7	0.15	0.15	1.2	0.3
16	8	1.5	5.0	75.0	20.0
33	7	0.5	10.0	75.0	2.5
75	9	0.15	40.0	—	5.0
73	8	0.15	40.0	—	0.3
68	7	0.15	40.0	—	5.0
22	7	0.15	40.0	20.0	10.0
63	6	0.15	40.0	—	0.6
76	7	0.15	20.0	10.0	0.15

*Listed in order in which discussed.

British soldiers who had received a booster one to five years, and in 3 of 11 whose last booster was five or more years previously. Wishart and Jackson[7] described only 1 such subject among 51 subjects retested three years after a booster injection of 10 Lf tetanus toxoid (approximately a standard booster dose), and 2 out of 61 who received one tenth this amount. Since our study was completed, Turner et al.[10] have reported the antitoxin levels found in 145 previously immunized Americans, mostly veterans of World War II. Nine out of 73 subjects, observed less than five years after the last injection of toxoid, exhibited titers of less than 0.1 u./ml. whereas 27 out of 72 manifested such levels five to eleven years after the last previous antigenic stimulus.

After this manuscript was completed, Peterson, Christie and Williams[11] reported on the persistence of antitoxin levels and the response to booster inoculations in over 200 veterans who had received their last previous toxoid one to thirteen years previously. They

found no subjects with titers below 0.1 u./ml. unless more than three years had elapsed since the last booster dose of tetanus toxoid. Only 2 of 187 subjects failed to exhibit at least 0.1 unit six or seven days after a booster. Both subjects had gone nine or more years since their last previous toxoid injections.*

TABLE 5. *"Protective Level" of Tetanus Antitoxin.*

SOURCE	YEAR	REMARKS
Estimates based on active immunization experiments*:		
Ramon[32]	1936	Cites Descombey as finding protection in horses with 0.001 unit
Sneath et al.[33]	1937	Spores; no deaths above 0.01 unit, occasional symptoms to >0.1 unit.
Cowles[34]	1937	Spores; animals usually survived at >0.05 unit, but some died with much higher titers.
Wolters & Dehmel[35]	1937	Spores; 2 animals survived with 0.02 & 0.05 unit.
Shumacker & Lamont[36]	1942	Toxin; some protection at 0.01 - 0.1 unit — more at >0.1 unit.
Zuger et al.[37]	1942	Spores; local tetanus in 7 pigs with >3 units; death in 1 with 3 units.
Estimates based on analogy with passive immunization:		
Sneath & Kerslake[38]	1935	Selects 0.1 - 0.25 unit
Gold[39]	1937	Selects 0.1 - 0.25 unit
Sachs[9]	1952	Selects 0.1 unit

*All experiments done in guinea pigs except those cited by Ramon.

In our study group, as noted above and demonstrated in Table 1, there was a fairly uniform scattering of subjects with titers below 0.1 u./ml. at all intervals studied; the total of such subjects was almost 25 per cent of the entire group. Somewhat over half this number had titers below <0.025 u./ml. Thus, it appears that, regardless of the interval since the last booster dose of toxoid, a certain proportion of such persons will be carrying an antitoxin titer that is within the range of scientific and clinical doubt and controversy. The controversy could be resolved if a clinically "protective level" of tetanus antitoxin could be established in man. Numerous efforts to do this by analogy have been made, along various lines of reasoning or of experiment. Table 5 summarizes the findings of the more rational attempts[9,12-19] to determine the "level of protection," either by animal experiments or by analogy with known protective ranges achieved by passive immunization. The breadth of choice is self-evident. Equally self-evident is the fact that no final answer is at hand. However, the ultimate criterion of effectiveness of tetanus immunization in man is its ability to prevent human cases of tetanus. Not only have the various immunization procedures used by the British, Canadian and American armed forces during and since World War II been extraordinarily effective, as noted at the beginning of this paper, but also there has been sufficient time to indicate that the occurrence of tetanus since World War II in American males twenty to thirty-nine years of age has shown a greater drop than that in any other age group except very young children.[20] In correlation with this finding, Ipsen[21] has demonstrated that in Massachusetts the number of males aged twenty to forty-nine, and especially thirty to thirty-nine, with very low tetanus-antitoxin titers is much less that that of males in other adult age groups or in adult females of any age group. This difference is unquestionably due to immunization associated with military service in this age group. To be sure, there will always be a small number of subjects (presumably similar to our subject 88) whose antibody response is defective. Their existence, however, will not alter immunization practices until methods for their ready identification are available.

Until such a test is available, clinical practice will require that a safe if arbitrary procedure be followed to establish and maintain a high degree of protection against tetanus. Our data do not offer any basis for determining what constitutes a maximum safe interval between booster inoculations; there seems to be little difference between three years and ten. However, it appears desirable not to adopt too long an interval because there may well be some tendency for a gradual fall in titer, not clearly detected in our study but suggested by the observations of Bigler,[8] Sachs,[9] Turner, Stafford and Goldman[10] and Peterson et al.[11] Moreover, too long a postponement of the inoculation may result in its being eventually ignored; also, there is some evidence[4] that the speed of response to a booster dose decreases after a number of years have elapsed since the last booster. Finally, it is well established that successive boosters tend to raise the antitoxin level higher and thus to ensure increased and generally prolonged protection against unrecognized or fulminating tetanus infection.

On the other hand, we see no indication for annual or biennial boosters, as has been the practice in some cases to our knowledge. Hence the four-year interval employed by the United States armed forces appears to be a suitable choice; there is, of course, no contraindication to moderate variations from this admittedly arbitrary interval, and it is likely that an extra booster in the first five years will provide additional protection, in view of the gain resulting from successive boosters noted above and found in the subjects examined by Peterson et al.[11]

Regarding the speed of response, Gold,[22] fifteen years ago, found that an antitoxin rise might be observed as early as the fourth day after a booster dose. Banton and Miller,[23] using fluid toxoid, observed the first rise on the fifth day, with all of 5 subjects responding by the sixth day. Miller et al.[4] found definite differences, depending on the type of toxoid used for basic immunization. However, with precipitated toxoid used for both basic and booster doses (as is widespread in civilian practice and required in military practice in the United States

*This interpretation is taken from the authors' tabular data, which are not entirely in agreement with their text.

today) a 100 per cent response was not obtained until the sixth day. Turner, Stafford and Goldman[10] observed a rise by the fourth day in a third of their subjects injected more than five years after the last previous toxoid, but only 4 out of 18 subjects with preinoculation titers below 0.1 u./ml. had reached such a level by that time. In contrast, 19 of 21 such subjects had titers of more than 0.1 u./ml. by the seventh day, and the other 2 had shown a definite rise.

Four of our 34 subjects with low preinoculation titers showed no appreciable rise when tested at the sixth day. However, the height of the six-day response had no relation to the interval since the last booster. Moreover, all subjects tested at subsequent intervals, except subject 88 and possibly subject 41, showed what appeared to be normal and adequate levels of antitoxin. Thus, our studies, like those of Bigler,[8] Turner, Stafford and Goldman[10] and Peterson, Christie and Williams,[11] indicate that the capacity to respond to a routine booster dose of tetanus toxoid is not lost for a decade and perhaps longer. Therefore, it may be concluded that a routine booster dose may be given with confidence at any time, at least within a decade of the last previous dose of toxoid *if immunization was previously completed.*

However, the data regarding the effectiveness of an emergency booster are not so clear cut, for, even if a 100 per cent response could be assured by six days, there is some question whether this would itself provide sufficient protection. There are occasional cases in which tetanus, even fatal tetanus, occurs despite the administration of an emergency booster dose.[1,4] It must be assumed that these subjects had low antitoxin titers and did not respond to the booster dose fast enough to mitigate the consequences of a fulminating tetanus infection. If they had had higher titers, clinical tetanus could scarcely have supervened. Moreover, in our study (Table 2 and Fig. 1), the response to a booster, in subjects with prebooster titers below 0.1 u./ml., appeared definitely poorer— as judged by actual titer reached — than that in subjects starting from higher preinoculation levels. The same finding has been made by Wishart and Jackson,[7] who conclude, "It would seem preferable to maintain an adequate level of antitoxin at all times by an accepted series of booster doses rather than to place sole reliance on the efficacy of a dose at time of wounding." The results of Turner et al.[10] are consistent with this conclusion.

There is growing reason to believe that the extreme rarity of tetanus in the American forces in World War II may have been due more to the establishment and maintenance of an adequate antitoxin serum level than to the use of the emergency booster. At any rate, it cannot be disputed that the existence of a measurable antitoxin level at the time of a tetanus-prone injury may provide better protection than a higher titer six days later. Hence, in general practice, dependence on the emergency booster dose after injury is probably of less importance than the maintenance of a persisting level of circulating antitoxin. This does not minimize the importance of the emergency booster, which, in persons with a known history of previously completed tetanus immunization, appears to be a valuable procedure for up to perhaps ten years after the last previous booster dose of toxoid. However, a civilian physician would be justified in giving simultaneous antitoxin prophylaxis to any patient who had not had a booster for over ten years or about whose immunization history he had the slightest uncertainty; to a patient whose injuries were around the head or neck and were multiple or extensively contaminated and hence most likely to lead to the fulminating type of tetanus; or to any patient whose treatment had been delayed more than twenty-four hours. The number of cases of tetanus prevented by such combined immunization rather than dependence on toxoid alone will probably be extremely small, and the risk of discomfort, immediate danger and possible ultimate allergic disease from the administration of heterologous antitoxin must be put into the balance. The judgment can best be made by the individual physician, who will know the conditions in his community regarding the likelihood of tetanus in relation to type and circumstances of the injuries suffered.

Summary and Conclusions

Tetanus-antitoxin titers were determined on 144 veterans of World War II at intervals of one to ten years after their last previous injection of tetanus toxoid. After the injection of booster doses of fluid or alum-precipitated toxoid, samples of blood were titrated at six, fourteen or twenty-one days, or one year later.

Antitoxin titrations showed that the levels of antitoxin were statistically identical in groups arranged according to intervals since last toxoid injection. The over-all geometric mean titer was 0.34 unit per milliliter. Thirty-five of 144 persons had less than 0.08 unit, and 14 had less than 0.025 unit per milliliter (the lowest value tested for).

Ninety-eight of 102 subjects tested at six days after a booster dose exhibited titers above 0.08 unit per milliliter. Of the 4 remaining, 1 had no later test, 1 had less than 0.2 unit after fourteen days and 0.025 unit after one year, and 2 had titers above 0.2 unit a year later (fourteen-day samples were not done).

All of 76 subjects with titers determined two or three weeks after a booster dose had levels above 0.1 unit per milliliter.

All but 1 of 68 subjects titrated a year after booster injection showed titers above 0.1 unit per milliliter. Ten subjects exhibited levels between 0.1 and 0.5 unit. This range may be adequate since studies by others suggest that after a year has elapsed since a

booster injection, the subsequent drop is much slower than the fall during the first year.

Out of 130 subjects on whom clearly interpretable postinoculation titers were obtained, 129 were demonstrated to respond to a tetanus-toxoid booster injection. The ability to respond was unrelated to the time elapsed since the last toxoid injection.

The relation of these findings to previously reported related findings of others is discussed.

Booster doses of tetanus toxoid should be administered routinely at fairly regular intervals, and four-year intervals appear satisfactory. A routine booster at any time up to ten years may restore immunity, and a booster dose of tetanus toxoid may be relied upon in an emergency in any fully immunized person up to ten years after the last previous toxoid injection. However, in the event of multiple, extensive or heavily contaminated injuries, especially about the head or neck, uncertainty regarding previous tetanus immunization or delay in administering the emergency booster injection, the simultaneous administration of antitoxin along with the toxoid is justified.

We are indebted to Dr. Francis B. Carroll, area medical director, Veterans Administration, for assistance and encouragement and to the Veterans Administration employees and Boston University medical students without whose cooperation this study could not have been made. Titrations were performed by Miss Anne Knudsen and Miss Mary Kane. The assistance of Corporal Irving Klugler, who carried out some of the statistical analyses, is acknowledged.

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PELVIC ENDOMETRIOSIS*

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ENDOMETRIOSIS is more frequently encountered today than heretofore. Its various manifestations and behavior are often the subject of comment and speculation. No completely satisfactory explanation of its etiology has been proposed, although several attractive theories have their ardent supporters. My own particular concern at this writing, however, is the treatment of the disease. More often than not, the decision in this matter must be made in the operating room, with neither patient nor surgeon prepared for the diagnosis. When the disease is extensive and has resulted in scarring and adherence of the pelvic viscera, either a small area is frequently excised for biopsy, or the uterus, tubes and ovaries are laboriously mobilized and removed. In young women anxious to remain fertile, neither of these choices is a happy one; the first procedure is often too little, and the second is unquestionably too much.

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Material

This paper reviews the details of management and the results of treatment in all cases of endometriosis encountered in the course of pelvic laparotomy on 400 consecutive private patients who came to operation for any cause. Endometriosis was found and the diagnosis histologically confirmed in 71 cases. The surgical prevalence was thus 18.1 per cent. In 22 patients the endometriosis, although proved by tissue examination, consisted exclusively of tiny black spots with scarring of the peritoneum. Its presence did

not influence the choice of treatment in these cases, and it must be considered purely an incidental lesion. This conclusion is strengthened by a glance at the range in age of this group: 17 of the 22 were over forty years old, and all had come to laparotomy for symptoms and findings of other gynecologic diseases. It is necessary to distinguish thus between incidental and significant endometriosis in any analysis of cases but particularly so here, where the emphasis is being placed on therapy.

In 49 patients pelvic endometriosis was the significant finding at the time of operation. Over half were between thirty and forty years of age, and only 10 were over forty. Hysterectomy was performed in 31 women, because either preservation of fertility at the risk of recurrence was not indicated or removal of the uterus was dictated by other disease. Endometriosis of the ovaries or peritoneum was frequently excised in addition to the hysterectomy, and in no patient in this entire group have the symptoms or the pelvic tumor recurred. Castration by removal of all ovarian tissue was carried out in only 8 of the 31 cases: in 2 because endometriosis also was present in the sigmoid, in 4 because both ovaries were extensively diseased, in 1 because of widespread involvement of pelvic peritoneum, and in 1 by reason of endometriosis in lymph nodes surrounding and obstructing the iliac veins, with edema and pain of the leg.

Of greatest interest is the group of 18 women in whom all areas of endometriosis were excised and fertility preserved. They were the youngest in the entire series, all being under thirty-five years of age except 1. Extent of disease, however, was never the deciding factor in treatment. Several had widespread involvement of ovaries and peritoneum, and 1 an endometrioma of the wall of the sigmoid with recurrent premenstrual incomplete obstruction. In the majority of cases surgery was completely successful and was followed by relief of pain and no recurrence of pelvic tumor. Four patients report gradual exacerbation of pelvic pain though only 1 has a palpable mass. Fifteen of the group have tried to conceive, and 4 women have experienced a total of 10 pregnancies, with 7 living children among them.

Technic of Operation

The details of operation for preservation of fertility have varied with the individual case. An effort has been made in each to excise all areas of disease and to re-cover the raw surfaces with peritoneum. Cysts, large or small, have been shelled out of the ovary, and the remaining normal tissue reconstructed into some semblance of its original state. Presacral neurectomy was also done in 10 of these patients, usually when pelvic pain was the outstanding symptom. The surgery in this group may be said to strive for radical conservationism, at the same time with an effort to remove all areas of endometriosis and to preserve the organs essential to reproduction. The operation does not qualify for the label "conservative surgery," which implies a minimum of dissection as well as of extirpation.

Discussion

This paper would present an incomplete picture of the disease if it failed to mention the patients in whom endometriosis was diagnosed without the confirmation of operation and pathological examination. In the period under consideration 15 women presented sufficient evidence in their clinical history and pelvic examination to justify the diagnosis. This is unquestionably a minimum figure, but a rigorous selection must be made if the conclusions are to be of value. Operation in most cases was delayed because no other diagnosis was seriously entertained, but in many the absence of severe pain and a deliberate effort to produce regression by pregnancy were also factors in the decision. Eleven patients tried to conceive, and 6 succeeded. This eminently satisfactory result in a small group of patients will encourage a future policy of surgical delay in women who seek to preserve fertility and in whom neither pain nor serious diagnostic difficulty compels a swifter solution.

The androgenic hormone, testosterone, has been used with effect, particularly in the patients not operated upon. Eight of these 15 women were given the drug, with marked relief of pain in 7; in 2 who reported inability to conceive for three to six years respectively, pregnancy followed within three months of testosterone treatment. Androgenic therapy also was used after surgery in 4 patients, but only 1 has conceived and the relation in this case is not so clear cut. The usual course of treatment has been 5 mg. of methyl testosterone sublingually daily for a hundred days; 10 mg. was used in some, and the course was repeated after an interval of months in 2 others. No patient showed virilizing changes or reported undesirable side effects of the medication. Normal menstrual cycles, with ovulation, continued throughout the treatment, and this was the strongest recommendation in favor of this program in lieu of others that seek to relieve the patient's symptoms by suppressing cyclic ovarian function.

Summary and Conclusions

Endometriosis has been found in 18 per cent of gynecologic laparotomies but it was the significant lesion in only two thirds of the cases. Hysterectomy, with excision of all areas of disease (but without castration except for special indications), is a dependable procedure for cure.

Excision of all areas of disease, without removal of uterus, tubes or ovaries, is usually sufficient to

relieve symptoms and will be followed by successful attempts to conceive in about a quarter of the cases. The application of a policy of radical conservationism in surgery is urged for patients in whom fertility is to be preserved.

Most fortunate of all are the women in whom the diagnosis could legitimately be made on clinical grounds and surgery delayed, for of this group over half were able to conceive. Testosterone administered sublingually has seemed to help in the relief of pain and perhaps also to enhance fertility.

MARKED HYPOGLYCEMIA ASSOCIATED WITH NONPANCREATIC TUMORS*

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OAKLAND, CALIFORNIA

THE association of nonpancreatic tumors with hypoglycemia is a rare and fascinating combination. In 1939, Seckel[1] reported a case of a fifty-six-year-old man with an eight-week history of episodes of unconsciousness that were finally recognized as attacks of hypoglycemia. The blood sugar on fasting and during attacks was usually between 26 and 44 mg. per 100 cc. and occasionally higher (72 mg. per 100 cc.). The seizures were stopped and prevented by administration of large amounts of glucose by mouth and parenterally. The alimentary glucose tolerance test showed a high rise, falling off to 30 mg. per 100 cc. at the end of two hours. The right leaf of the diaphragm was noted to be elevated on x-ray examination. On the basis of a clinical diagnosis of hypoglycemia, presumably from a pancreatic adenoma, the patient underwent an exploratory laparotomy. No pancreatic adenoma was found, and the liver appeared normal. Postoperatively, the patient failed to recover consciousness despite the administration of 300 gm. of glucose parenterally. At autopsy a massive fibroma was found superior to the right lobe of the liver, bulging against the medial aspect of the right leaf of the diaphragm. The pancreas was normal, and no metastases were observed. An assay of the fibroma was negative for insulin.

In 1942 Arkless[2] reported the case of a forty-five-year-old man with a history of convulsive seizures. Investigation revealed a subphrenic mass on the left that was removed and found to be a 2000-gm. rhabdomyofibroma arising from the diaphragm. No further seizures occurred until the patient was admitted to the hospital seven years later with a maniacal, noisy manner that was noted to be improved after eating. The fasting blood sugar was 30 mg. per 100 cc. He was being managed for a while on a high-carbohydrate diet, when he suddenly died. Autopsy showed a 2700-gm. spindle-cell sarcoma in the left chest cavity, which pushed the left leaf of the diaphragm downward. Except for a small lymph node in the abdominal cavity, there was no other evidence of tumor. The pancreas and liver were normal.

Hines,[3] in 1943, described a forty-two-year-old man with spells of weakness and stupor relieved by orange juice. The fasting blood sugar varied from 30 to 56 mg. per 100 cc. A laparotomy revealed a large sarcoma in the right upper quadrant adherent to the right kidney. For two years after removal of the tumor there was no hypoglycemia. He then began to have attacks of hypoglycemia controlled by orange juice and died shortly afterward. Autopsy revealed ascites. Half the right lobe of the liver was replaced by necrotic tumor tissue, and the left lobe was hypertrophied. The pancreas was normal.

In 1949, Rosenfeld[4] reported 2 cases of hypoglycemia associated with peritoneal pseudomyxoma. The first patient was a forty-six-year-old man who, three years after laparotomy for what was thought to be generalized abdominal carcinomatosis, had five episodes of coma. During the first episode the blood sugar was 50 mg. per 100 cc. He recovered consciousness in a few minutes after being given 25 gm. of glucose intravenously. Blood sugar determinations were not done during similar later episodes, but the response to intravenous infusions of glucose was always prompt. The hypoglycemic episodes disappeared when it was no longer necessary to withhold food for diagnostic studies. Seven months later he died of intestinal obstruction and pneumonia. Autopsy revealed large cystic tumors throughout the abdominal cavity. The pancreas was normal. Grossly, the liver appeared normal, but microscopical examination disclosed numerous dilated sinuses with necrotic cells.

Rosenfeld's second patient, a fifty-one-year-old man, had a blood sugar of 60 mg. per 100 cc. on one occasion and 30 mg. per 100 cc. on another. No mention was made of hypoglycemic episodes. At operation this patient was found to have ascites and large, multilocular cysts in the abdomen. Postoperatively, he died of pneumonia. An autopsy was not performed.

The following case is somewhat similar to those of Seckel[1] and Hines.[3]

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The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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Case Report

B.G.H. (U.S.N.H. 226901), a 23-year-old man, was in good health until July, 1953, when his wife first noted a change in his personality. During the following month he experienced a feeling of weakness when he awakened in the morning and once fainted while shaving. By November he was having difficulty in awakening in the morning and had periods of marked confusion. On December 11 he was hospitalized in a naval hospital because he was confused, withdrawn and negativistic. The original impression was schizophrenic reaction. On December 19 he was transferred to the Psychiatric Service of the United States Naval Hospital, Oakland, California, for further study. When originally seen he had complete amnesia for the periods of confusion in the past. After admission he became steadily more unresponsive and withdrawn. On the morning of December 30 he was found to be in a coma. When seen by a medical consultant he had a mass in the right upper quadrant. An emergency blood sugar was 35 mg. per 100 cc. He was given 30 cc. of 50 per cent glucose, intravenously and rapidly, and within 15 minutes had recovered full consciousness. That afternoon he was transferred to the Medical Service for diagnostic studies. He was then entirely lucid, and a review of the systems was negative except for the history of recurrent morning weakness. He had amnesia for the periods of personality change.

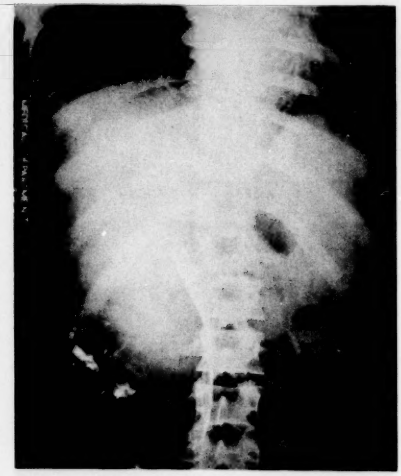

Figure 1. *Retrograde Pyelogram on the Right Side. Note the marked medial displacement of the ureter and calcification in the tumor.*

Physical examination revealed a pleasant, slender man. Examination of the eyes, ears, nose and throat was negative. There was no lymphadenopathy. The heart and lungs were normal. There was some impairment of movement of the left leaf of the diaphragm. In the right flank there was a very large, hard mass that was palpable anteriorly and posteriorly. It did not move with respiration. The liver and spleen were not palpable. In the right upper quadrant, separate from the large mass, was a firm, ovoid lobular mass, 10 by 6 cm. in size, that barely moved with respiration. There was no jaundice. Rectal and neurologic examinations were negative.

The blood pressure was 120/80, and the pulse 90.

The blood Kahn test was negative. The hemoglobin was 13 gm. per 100 cc., and the white-cell count 7550, with 65 per cent neutrophils, 28 per cent lymphocytes and 7 per cent eosinophils. The urine was negative for sugar, albumin, and abnormal sediment; it was faintly positive for urobilinogen. An electrocardiogram was normal. X-ray study of the chest was negative. A scout roentgenogram of the abdomen showed a large mass in the right upper quadrant, containing some small calcifications.

On December 31 the patient became deeply stuporous, responding only to painful stimuli. Deep-tendon reflexes

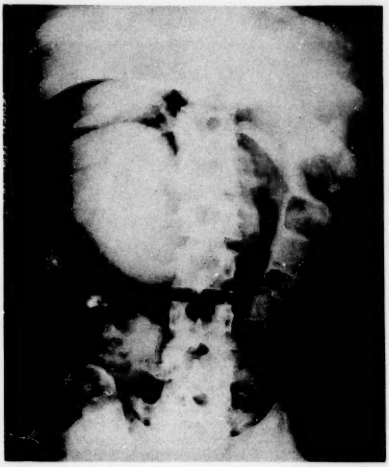

Figure 2. *Roentgenogram Taken after Retroperitoneal Oxygen Insufflation, Outlining the Tumor Mass.*

were hyperactive, with clonus bilaterally and positive plantar reflexes. A blood sugar drawn immediately was 32 mg. per 100 cc. The patient was rapidly given 50 per cent glucose intravenously. After 20 cc. had been administered he opened his eyes suddenly; after 50 cc. he was responsive, answered questions, and his neurologic status had reverted to normal.

On that day, retrograde pyelography and retroperitoneal air-insufflation studies showed the large mass in the flank to be extrarenal (Fig. 1 and 2). The small, firm mass in the right upper quadrant was shown to be the right kidney, which was displaced up to the anterior abdominal wall by the mass in the flank.

Control of the hypoglycemia was accomplished with the continuous administration of glucose by gavage and intravenous infusion. Approximately 400 gm. of glucose was given daily during the 4 days before operation.

It was not believed that the patient had an islet-cell tumor of the pancreas because of the flank location of the mass. The diagnoses considered preoperatively were: islet-cell adenoma or carcinoma arising in aberrant pancreatic tissue and a retroperitoneal tumor of nonpancreatic origin causing unexplained hypoglycemia. (We were aware of Seckel's case before operation.)

On January 4, 1954, with the patient in the left lateral decubitus position, an incision was made over the course of the right 12th rib and continued anteriorly to the lateral margin of the right rectus muscle. The 12th rib and a 2-cm. section of the posterior portion of the 11th rib were resected. The oblique abdominal muscles were divided, and a large-bladed Finochietto retractor was placed against the brim of the pelvis and the 11th rib. The peritoneum and the right kidney and ureter, which were displaced anteriorly to a position immediately beneath the right rectus muscle,

were mobilized medially. A huge ovoid retroperitoneal tumor occupied the entire right posterior portion of the abdomen (Fig. 3). The tumor mass was encapsulated anteriorly, medially and laterally. It was firm and very vascular. It involved the entire iliopsoas muscle. The dissection around the periphery of the encapsulated tumor was simple until the iliopsoas muscle was encountered posteriorly. Inferiorly, this muscle was divided at its point of emergence from the pelvis.

A mechanical difficulty now presented itself: the tumor mass filled the operative field, and it was not possible to clamp the broad origin of the psoas muscle posteriorly.

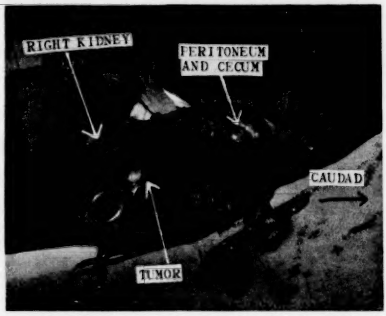

FIGURE 3. *Photograph Taken at Operation with the Patient in the Left Lateral Decubitus Position. The hemostats are 30 cm. long.*

Therefore, it was necessary to divide the origin with long scissors, remove the tumor mass and control the massive hemorrhage with packs, followed by individual clamping of the markedly enlarged branches of the lumbar arteries. When hemostasis had been established it was noted that the tumor extended posteriorly between the transverse processes of the 1st, 2d and 3d lumbar vertebras. This portion of the tumor could be resected only through a posterior approach at a later date. Several small arterial branches retracted within the intervertebral foramens, rendering their clamping impossible. The comparatively mild bleeding from these vessels was controlled with a gauze pack, which was brought out through the posterior angle of the incision. The patient withstood the operation well and at no time became hypotensive. The measured blood loss of 6000 cc. was replaced with whole blood during and immediately after the surgical procedure.

The postoperative convalescence was uneventful except for a draining sinus tract that followed the removal of the gauze pack. Interestingly enough, the glucose requirement reverted to normal immediately after the operation, and 8 days later glucose tolerance was normal.

On March 15 a lumbar myelogram revealed an elliptical enlargement within the spinal column extending from the 1st to the 3d lumbar vertebra on the right. Neurologic examination was negative, and the patient was asymptomatic.

On March 15 a lumbar laminectomy was performed. The spinous processes of the 1st and 2d lumbar vertebras were removed. The interlaminar ligament was separated from the lamina of the 2d lumbar vertebra, and the laminas of the 1st, 2d and 3 lumbar vertebras were resected. The varicolored tumor mass presented under the lamina of the 2d and extended up under the 1st lumbar vertebra. It had entered the spinal canal through the intervertebral foramens. It extended over the posterior aspect of the dura, and also extended anteriorly and along the course of the nerve root that branched off at the 2d lumbar segment on the right. All visible tumor was removed. The dura was not entered. Convalescence from this operation was entirely uneventful.

On gross examination the specimen weighed 1200 gm., consisting of a large, lobulated mass of rubbery, firm tissue, encapsulated by a paper-thin, fibrous tissue. Numerous large blood vessels were seen coursing through the tumor. A considerable amount of muscle tissue was attached to one side of the tumor. On section, it was tawny to yellowish-brown. Some areas contained firm, circumscribed zones, and in others there was palpable calcification. Numerous sections taken from various areas revealed the same histologic pattern (Fig. 4). The tumor was composed of tissue that suggested fibrous-tissue origin. Some areas were extremely cellular, and the cells in these areas were round to oval, with prominent nucleoli and long cytoplasmic processes. Only rare pleomorphic forms were present. In the less cellular areas the cells remained uniform, and the matrix was of a looser texture; in other areas the tissue was more hyalinized. Special stains, including those of Nissl, van Gieson, Laidlow and Davenport, indicated that the tumor was of mesodermal rather than neural origin, probably arising from fascia rather than muscle. The pathological diagnosis was retroperitoneal fibroma.

An assay of the tumor for insulin was not done.

The patient has been followed by the Tumor Board of a Veterans Administration Hospital in Texas during the past year. The latest report, 18 months after removal of the tumor, stated that he was asymptomatic, that there was no evidence of recurrence and that no hypoglycemic episodes had occurred. His weight has been stable, and he has been at work.

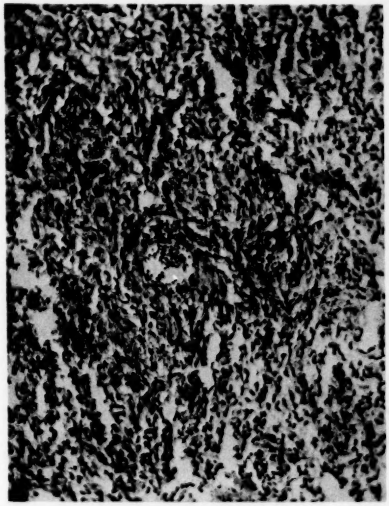

FIGURE 4. *Photomicrograph of the Tumor.*

DISCUSSION

In his scholarly presidential address to the American Surgical Association in April, 1955, Gibbon[5] stated that a certain portion of each period of instruction should be devoted to things that are not known. Certainly, the physiologicopathological condition involved in the production of severe hypo-

glycemia by large, nonpancreatic tumors can be classified as unknown.

Various explanations have been offered for the association of hypoglycemia with large tumors in the few reported cases. A great hunger of the tumor for glucose has been suggested; however, Woodward and Fry[6] found that patients with carcinoma had an average blood sugar of 20 mg. per 100 cc. — higher than that of normal controls. The association of hypoglycemia with tumors is extremely rare, and it is well known that patients with massive carcinomatosis are not hypoglycemic. In the case presented above, as in those of Seckel[1] and Arkless,[2] hepatic failure was certainly not associated with the tumor.

The common denominator of all reported cases appears to be that the tumors were large, that the viscera were displaced and that pressure was produced on the posterior abdomen or thorax. The location and histopathology of the tumors varied. It is possible that the hypoglycemia was caused by some pressure, stretching or disruptive effect on unknown receptors in the abdominal cavity. Evans and his coworkers[7] reported that disruption of sympathetic impulses to the liver of a cat can cause hypoglycemia. In any event, an important but presently unknown physiologic mechanism in the control of blood sugar may well be involved.

Summary and Conclusions

The literature is reviewed, and the 5 previously reported cases of hypoglycemia associated with nonpancreatic tumors are summarized.

A case of severe hypoglycemia associated with a large retroperitoneal fibroma is presented. Removal of the tumor cured the hypoglycemia.

Possible causes for the altered physiology are discussed. An unknown mechanism for the control of blood sugar may be involved.

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SPECIAL ARTICLE

THE EARLY HISTORY OF SURGERY FOR COMMON-DUCT STONES

A Brief Review

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In 1884 Tait[1] gave the following description of his efforts to extract common-duct stones:

> It is clear I shall not succeed in this way, and I propose to open the abdomen again, about an inch to the inner side of the gall-bladder, and crush the stone in situ by means of padded forceps applied outside the duct. If a better plan should occur to any of my readers I should be glad to have it, and if it should be practicable and successful, its originator shall have full credit for the suggestion.

In the same year, Langenbuch[2] suggested "opening" the common duct, and ten years later, after many personal experiences with choledochotomy, Kehr[3] declared that stones in the common duct should be removed by "incision in the duct."

In the intervening period (1884-1894) surgery for common-duct stones evolved as a necessary and logical sequence to surgery directed at the gall bladder. On the other hand, many of the leading surgeons and physicians of that time agreed with Hirschberg,[4] who warned that "operative interference was not allowable while a stone is demonstrably or probably passing through the duct." This point of view was given support by the high surgical mortality resulting from hemorrhage and "cholaemia," in cases in which common-duct stones were present.

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Procedures Recommended

There were several reasons, however, why surgeons, during the final twenty years of the nineteenth century, were forced to deal with stones in this particular location. Since Charcot's classic description of the symptoms peculiar to common-duct stones had only appeared a few years before, in 1877, and because many cases of choledocholithiasis did not conform to this description, there were frequent chance meetings with this type of biliary disease during a cholecystotomy. Furthermore, medical measures to dissolve biliary calculi or to purge them "often" failed, and the long-suffering patients became hopeful seekers of the last resort. Finally, as suggested by Tait's[1] comment,

quoted above, attempts to close persistent external biliary fistulas and to ignore the causes of biliary fistulas met with failure. It is not surprising that several methods of handling this complication were developed, each adding and contributing to the endeavor to relieve obstruction to bile flow.

The creation of an external biliary fistula might very well transform an often hopeless situation into one in which a pint or more of bile flowed out daily through the sinus tract. With improvement in the patient, and perhaps with the aid of "spring-water," the stone might be passed. If not, a second procedure aimed directly at extracting the stone could be performed as proposed by Tait and later by Parkes.[5]

One could attempt to push movable common-duct stones through into the duodenum, as suggested by Handfield-Jones[6] in 1878, or back up into the gall bladder, which, according to Musser and Keen,[7] would be "more likely to succeed, for this part of the ducts has already been dilated by their onward passage." In 1887 Thornton[8] described 2 cases in which he successfully removed common-duct stones. After instrumentally dilating the cystic duct through the opened gall bladder, he crushed the stones with a forceps and removed the remaining particles. These stones were "immovable" ones, and this method was designated as direct cholelithotripsy as opposed to that advocated by Tait in which an indirect crushing was effected. On July 12, 1884, Tait[9] reported that a stone the size of a cherry in the patient mentioned in the first paragraph was crushed by "two strokes of the forceps." Kocher,[10] however, preferred to use his fingers to crush common-duct stones and relates that in 1 patient, on the eighth day after this manipulation, "there was an evacuation from the bowels containing the fragments of stones and normally colored with bile."

Nussbaum is said to have suggested biliary-intestinal anastomosis as a possible answer to the problem of common-duct obstruction, and in the same year (1882) Gaston[11] reported a series of successful cholecystenterostomies in dogs. Two years later von Winiwarter[12] recorded the first successful example of a cholecystenterostomy on a patient with a "permanent block" in the common duct. He performed a cholecystocolostomy in "six sittings." Cholecystenterostomy soon became a frequently used procedure.

The limitations of the foregoing measures became apparent within a few years to those who applied them. Frequent sequelae were retained stones, damage to the duct, persistent external biliary fistulas, bouts of hemorrhage and liver failure. Five years elapsed between Langenbuch's advice to attack the problem directly by incision in the duct and its first successful application in 1889. Kummell,[13] however, reported in 1890 that "many years before" he had opened the common duct and removed the gall bladder of a patient who died twenty hours after a long and arduous procedure.

Choledochostomy

There is not general agreement even today who should receive the credit for the first successful choledocholithotomy. Courvoisier,[14] Thornton,[8,15] Marcy[16,17] and a few others have been accredited at one time or another. In 1898 an interesting exchange of letters about priority in this matter occurred, Fenger[18] championing Courvoisier as the first, and Marcy[19] claiming recognition as the pioneer. No conclusions were reached by either, but, as often happens, neither proved to be correct. In England Thornton[15] had already performed 2 successful choledochostomies with removal of common-duct stones in May and June, 1889, a full four months before Marcy and seven months before Courvoisier had attempted similar procedures. Also, Heussner,[20] in June, 1889, performed a similar operation, with good results. In 1893 Abbe[21] recorded a successful choledochostomy that had been done in April, 1889. Courvoisier, nevertheless, gave a clear indication of his knowledge of the clinical and pathological characteristics of common-duct calculi, for he was the first (January, 1890) to operate expressly for this complication in a patient who had undergone a cholecystectomy previously. It is understandable, therefore, why some have discounted the 7 cases done before 1890 in favor of this "choledochostomy only" operation of Courvoisier's.

Moderate detail is available concerning the 2 cases of choledochostomy performed in this country in 1889. Abbe[21] described his patient as follows:

> . . . a lady aged thirty-six . . . had gone deeper in sickness after her first attack of gall-stone colic, two and a half years before. She had become almost a black green, had lost thirty pounds, had progressive indigestion and vomiting. She had stools entirely devoid of color and urine like porter. Her paroxysmal pains were terrible and petit-mal had been recurrent daily for two months. The urine had five per cent of albumin and some hyaline casts . . . On doing laparotomy [on April 13, 1889] I found the gall-bladder buried in adhesions to the stomach, omentum, and colon, but not distended. Several gall-stones were removed from the incised viscus, and a large one found more than half way down the common duct, absolutely immovable. I cut the common duct open and took out the stone, then removed the damaged gall-bladder and putting a large drain-tube into the hepatic duct sewed up the common duct with fine silk. Around the drain that emptied the hepatic duct I put a larger one . . . The patient lost all her bile through the tube for five days. The inner tube was removed on the second day and the sinus closed in three weeks. The patient maintains perfect health to date (March 1893) having in four years had the felicity of bearing a much hoped-for boy.

Two illustrations accompany this case report (Fig. 1).

On October 26, 1889, in Cambridge, Massachusetts, Marcy operated on a forty-year-old woman with a history of several attacks of biliary colic of a serious character, accompanied by jaundice. His description of the case follows:

> Immediately upon dividing the peritoneum, the cystic growth (gall-bladder) distended the lips of the wound. It was attached to the peritoneum by a double row of tendon sutures and incised. Ten ounces of thin, light

colored bile escaped, floating out with it a gall-stone the size of large almond. Careful probing revealed the presence of another calculus in the common duct. All effort at dislodgement failed and as much force as was deemed justifiable was used in the attempt to crush it but without avail . . . [After further manipulation had failed] I then divided the walls of the duct with scissors, and everted its edges from over the roughened calculus which was even then removed with difficulty. The thickened mucous membrane of the duct and bladder was joined by a fine continuous tendon suture . . . Rapid convalescence ensued without incident and the patient remains vigorous and active (May, 1890).

A longhand report of this experience can be found in Marcy's Case-Book of 1889.[22]

Three years later, Kocher found himself in a similar situation when he discovered a stone the size of a pigeon's egg in the choledochus behind the duodenum:

The stone was very hard and it was impossible to crush it with the forceps. The middle left finger of the operator was placed behind the stone and the duodenum, lifting them up. An assistant pressed the duodenum down upon this finger from above. The anterior wall was then cut transversely across its entire width; then an incision was made longitudinally through the posterior wall and the choledochus, so the stone could be removed. The choledochus was then sewn to the wall of the duodenum

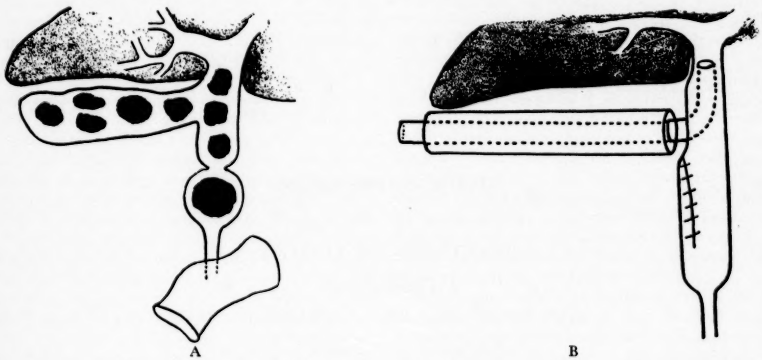

FIGURE 1. *Location of Stones* (A) *and Method of Common-Duct Drainage* (B) *(Reproduced from Abbe*[21]*).*

Following on the heels of these efforts by Abbe and Marcy and the ones by Thornton,[15] Kummell[13] and Heussner,[20] were the three dramatically successful choledocholithotomies in early 1890 by Courvoisier.[14] It was largely due to his influence that incision of the duct quickly became the procedure of choice when common-duct stones were palpated. Osler's[23] report on the grave natural history of patients with common-duct obstruction further emphasized the need for early surgical intervention.

It remained for McBurney[24] and later Kocher[25] to elucidate means whereby stones in the lower portion of the common duct could be extracted. Faced with just such a problem in the year 1892, and unable to bring the lower end of the common duct into view, McBurney "made a vertical incision, about one and a half inches long" in the anterior duodenal wall directly opposite the entrance of the common duct:

A probe was introduced without difficulty which, after passing about half an inch, came in contact with a firmly impacted stone. The orifice of the duct was first slightly incised then with the aid of forceps largely stretched until it was possible without difficulty to dislodge the calculus and draw it down into the intestine. Large quantities of bile flowed into the duct. The wound in the intestine was then sutured with three rows of silk . . . forming a fistula between the two, and the anterior wound was closed.

DISCUSSION

The successful outcomes in these 2 patients demonstrated that the entire extrahepatic biliary tree could be explored satisfactorily. In 1896, Fenger,[26] in a marvelous paper, described surgery of the common duct in all its facets, including the ball-valve action of many common-duct stones with resultant intermittent obstructive symptoms. Over the past sixty years numerous advances in surgery for common-duct calculi have resulted in a decrease in the operative mortality from 18 per cent[27] in 1895 to between 1 and 2 per cent at the present time. A broadening of the indications for exploring the common duct, more accurate preoperative evaluation and preparation, and improvements in technic are three of many reasons why choledochostomy has become an essential feature of the biliary-tract surgery of today.

SUMMARY AND CONCLUSIONS

The early history of surgery for common-duct stones is reviewed, and its logical progression to the concept of incision of the duct is demonstrated.

Although the choledocholithotomy performed by Kummell preceded all others by at least five years, the first successful one was performed by Abbe (April, 1889). McBurney introduced duodenotomy as an approach to the terminal portion of the common duct (1892). The operations of Marcy and Kocher bear an interesting relation to the subject.

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MEDICAL PROGRESS

TREATMENT OF LEPROSY

I. Chemotherapy

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THE terminology of leprosy has changed considerably in recent years, making necessary some account of the present classification of the disease. Two principal types are recognized, lepromatous and tuberculoid, and two intermediate groups, indeterminate or uncharacteristic and borderline (dimorphous). The main types vary greatly in relative frequency in different parts of the world. In the Philippines, for example, lepromatous cases constitute perhaps 40 per cent of total leprosy; in India, this form accounts for only about 20 per cent. Of indigenous cases arising in the continental United States, about 85 per cent are lepromatous.[1]

The lepromatous type is characterized clinically by diffuse infiltration of the skin, which becomes thickened, glossy and corrugated. Localized infiltration may appear as macules or plaques with ill defined borders, sometimes exhibiting disturbance of sensation. Nodules may develop in normal or infiltrated areas. *Mycobacterium leprae* is readily demonstrable in smears, and the histologic structure is granulomatous, with "globi" and typical foamy "lepra cells." Lymph nodes, spleen and bone marrow[2] are invaded. Involvement of the nasal mucosa is common, and extension to the nasopharynx, trachea and larynx may be a serious complication in late stages of untreated cases. Bacillary invasion of the eye is frequent and extremely serious. Certain peripheral nerves are invaded sooner or later — notably, those of the extremities, with consequent anesthesia, atrophy and deformity, the damage in the end often being equal to that of the tuberculoid type. The patient does not react to intradermal injection of killed leprosy bacilli (lepromin test), and the disease is progressive.

In the tuberculoid type the characteristic macules (leprides) are erythematous, show clearing at the centers and have well defined, often papulated, edges. Anesthesia is invariably present and usually well marked in these macules. *Myco. leprae* is rarely found in smears from the quiescent lepride, but may be present in great numbers during reaction. The histologic structure shows many epithelioid cells with large nuclei and giant cells of the Langhans type. Involvement of the peripheral nerves is early and marked, and damage therefrom constitutes the most serious feature of this type. The patient reacts to

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lepromin, and the disease is characterized by long periods of remission, often punctuated by episodes of reaction during which additional nerve damage takes place.[3]

If flattened skin lesions of a suggestive nature are present but the histologic findings are those of simple inflammation, the case may be classed as indeterminate. Smears are seldom bacteriologically positive, and the lepromin test may be positive or negative. The borderline group includes cases in which the macules show the clinical and histologic features of both principal types. Smears are usually positive and the lepromin test negative.

Success in treatment of many infectious diseases has been attained primarily through the agency of the experimental laboratory. Antibiotics and drugs are screened for their lethal effect against the causative micro-organism in vitro or for their repressive or curative effect in artificially induced disease in an animal. Unfortunately, neither of these procedures is as yet possible in leprosy. The only scientific therapeutic approach at present available is the trial of the drugs or antibiotics that have proved effective against other micro-organisms having certain fundamental characteristics in common with *Myco. leprae*. For this reason great attention has been given to drugs that are active against *Myco. tuberculosis*. There has also been much experimental therapy in so-called murine leprosy, caused by *Myco. leprae murium*. This bacillus cannot be cultivated in vitro, but the disease can readily be maintained in the laboratory animal by successive inoculations of infected tissue.

The nature of leprosy makes it essential that therapeutic trials be adequately controlled; otherwise, remedies that have value, but fall short of complete success, may pass undetected. The natural course of the disease is prolonged over many years, with a tendency to exacerbation and remission. Clinical changes that are rapid and readily observable may occur, but usually they are of slow evolution, especially in the lepromatous type. In this type, bacteriologic changes are likewise slow, and their measurement difficult. Finally, there is no method for distinguishing active, multiplying leprosy bacilli from those which may be damaged or dead.

The history of the treatment of leprosy with chaulmoogra oil is illuminating. For generations this oil was the popular remedy, and its esters and other derivatives were in world-wide use for half a century.[4] Hundreds of favorable case reports appeared, with photographs before and after therapy, and imposing statistics of arrest of the disease. Controlled studies were not made, and probably became impossible to make, so universal did faith in the remedy become. Consequently, any value that chaulmoogra oil may have in leprosy has not been established. Its use has been gradually abandoned during the last decade.

The Sulfones

In the sulfone group of drugs ($R\text{-}SO_2\text{-}R$) the sulfonyl radical is combined with two carbon atoms whereas in the sulfonamides ($R\text{-}SO_2\text{-}NH_2$) this radical is combined with one carbon atom and an amino group.[5] It is of historical interest that the so-called basic sulfone, 4-4′ diaminodiphenyl sulfone (DDS), was synthesized in 1907 by Fromm and Wittmann but was not tried in infections of animals until 1937. Activity was demonstrated against tuberculosis in guinea pigs, but it was considered too toxic for human use.

In 1941, after promising results in experimental tuberculosis obtained by Feldman, Hinshaw and Moses[6] at the Mayo Foundation, a sulfone was first used in the treatment of human leprosy by Faget and his associates[7] at the Public Health Service Hospital, Carville, Louisiana (National Leprosarium). The drug was glucosulfone sodium, synthesized at Parke, Davis and Company and called Promin. This proved too toxic for oral use but was well tolerated when given intravenously. Soon afterward, sulfoxone sodium (Diasone) was synthesized simultaneously at Abbott Laboratories, and the National Institutes of Health,[8] found to be suitable for use by mouth and reported to be effective by Muir[9] in Trinidad. Many other preparations for oral use followed.

The original report of Faget and his associates[7] mentions a small study of a sulfone in which patients considered comparable were left untreated as controls. Limited information is given concerning clinical changes, and nothing regarding bacteriology. Promacetin (synthesized by Parke, Davis and Company), then called Internal Antiseptic No. 307, was given to 20 patients in doses of 0.3 to 1.0 gm. daily. A placebo was given by mouth to the same number of patients, matched for type and stage of disease. After eight months the condition of the Promacetin group was considered to be superior, judged on the basis of ulceration, rhinitis and laryngitis.

Arnold[10] comments that it is curious, in the chemotherapy of leprosy, that the same return to the parent drug has occurred as happened in the chemotherapy of syphilis with a return to oxyphenarsine hydrochloride — namely, a return to DDS initiated by Cochrane[11] in India. In leprosy the principal factor was much lower cost of DDS than of the higher compounds. Cochrane used an intramuscular injection in peanut oil of not more than 1.5 gm. weekly. In Nigeria, Lowe[12] has given, with safety and effectiveness, oral doses of not more than 0.3 gm. daily. In the first series of the Leonard Wood Memorial clinical evaluation studies[13] no toxicity was observed with a daily dosage of approximately 0.2 gm. continued for forty-eight weeks.

The activity of the sulfones in leprosy is often attributed to liberation of DDS. This is true of Promin,

Diasone, Sulphetrone (synthesized by Burroughs Wellcome and Company) and other disubstituted compounds, which have a substituent in each amino group, when given orally; however, only small amounts of DDS are found in the blood or urine when they are administered parenterally. Monosubstituted compounds with one free amino group, such as hydroxyethyl sulfone (HES), and nuclear substituted derivatives with two free amino groups, such as Promacetin, do not break down to DDS — that is, they act as entire molecules, regardless of the route of administration. There is no clear indication that any sulfone compound is more effective than another in the therapy of leprosy.

Slowness of action has been a recognized handicap of the sulfones since they were first tried. A report by Erickson[14] of the late results of therapy at Carville has emphasized the need for more rapid and effective treatment and for a bactericidal drug. He studied the probability of arrest under sulfone therapy, defined as a one-year period of negativity of smears from skin and mucous membranes and of freedom from clinical evidence of activity of the disease. He found that it increased from 3.6 per cent by the end of the second year of treatment to 73.0 per cent by the end of the ninth year. Relapse occurred in 6 of 33 patients who were followed for one to five years after apparent arrest.

Dihydrostreptomycin and Sulfones Singly and Combined

Since 1951 carefully controlled therapeutic trials of sulfones and other drugs in treatment of the lepromatous type have been conducted by the Leonard Wood Memorial.[13] In the first series, 6 comparable groups at each of 4 leprosariums — 2 in Japan, 1 in the Philippines and 1 in South Africa — were placed respectively on Diasone; DDS; dihydrostreptomycin sulfate (DHSM); DHSM and Diasone; and DHSM and sodium para-aminosalicylate (PAS) and a control drug. The Diasone and DDS tablets were identical in appearance; each of the latter contained 0.065 gm. of DDS, which is the approximate molecular equivalent of the DDS in the absorbed part of each Diasone tablet of 0.3 gm. Full dosage of each was 3 tablets daily. The dosage of dihydrostreptomycin was 1 gm. three times a week, and that of PAS 15 gm. daily. In Japan and the Philippines the control drug was a placebo (CESLU), resembling DHSM and also given intramuscularly three times a week, containing small amounts of inositol and glycine. In South Africa the control group was given PAS. The duration of the experiment was thirty-two weeks at the Japanese institutions and forty-eight weeks at the others. A total of 960 patients entered, and 852, including those withdrawn because of worsening of leprosy, completed therapy. The clinical status of the patients was checked before and after therapy by an outside consultant who was kept in ignorance of the treatment given individual patients.

Clinical improvement occurred in about the same proportion of each of the 5 therapy groups at each institution. In Japan and the Philippines much higher proportions of the controls than of the other groups became worse. In South Africa the control (PAS) group did about as well as the others. Studies of smears from eight body sites before and after therapy showed that a considerable proportion (about 40 per cent) of sites containing a few bacilli at the outset became negative, but this was true of all groups, including the controls, at all institutions. Sites in which many bacilli were present before therapy rarely became negative in any group. There was no significant improvement in the neurologic picture in any of the patients, nor did it appear that earlier cases profited more from therapy than those in which the disease was advanced, but it should be stated that few truly "early" infections were included in the study.

It was concluded that Diasone, DDS and DHSM are of about equal value so far as judgment can be made after forty-eight weeks of therapy. The results were disappointing in that combined treatment with Diasone and DHSM, or with DHSM and PAS, offered no advantage.

Isonicotinic Acid Hydrazides Singly and in Combination with Sulfones or DHSM

After reports of effectiveness of isoniazid in tuberculosis in 1952, Dr. J. N. Rodriguez, of Manila, under the auspices of the Leonard Wood Memorial, treated 3 matched groups of 25 lepromatous patients each at the Central Luzon Sanitarium, the first with DDS, the second with isoniazid, and the third with Marsilid (synthesized by Hoffmann–LaRoche), an isopropyl derivative of isoniazid, for a period of twenty-four weeks. The clinical condition of the patients was appraised before and after therapy by Dr. C. B. Lara, of the Culion Sanitarium. The proportions improving, or worsening, were almost the same for the 3 groups. Bacteriologic results, likewise, showed no material differences. A similar study in which 21 lepromatous patients on isoniazid were matched against the same number on CESLU was conducted at the same time by Dr. J. G. Tolentino at Eversley Childs Sanitarium, Cebu, Philippines; the assessor was Dr. J. N. Rodriguez. At the end of thirty-two weeks the patients receiving isoniazid, taken as a group, were in better clinical condition than those on CESLU. The results, however, appeared to be definitely inferior to those with either Diasone or DDS. The clinical impressions of others who have used isoniazid or its derivatives are in general agreement with this conclusion. At Carville Marsilid was abandoned after eleven months' trial in 27 cases of lepro-

matous leprosy, 2 of the tuberculoid type and 1 indeterminate. In all but 2, which showed slight clinical improvement, the disease was unchanged or definitely worse. Smears yielded no evidence of reduction in the numbers of *Myco. leprae.*

It remained to test the value of isoniazid in combination with other drugs, especially sulfones and dihydrostreptomycin. This was done in the second series of the clinical evaluation studies of the Leonard Wood Memorial. At each of 3 leprosariums, 2 in the Philippines and 1 in South Africa, 3 comparable groups of lepromatous patients were placed respectively on Diasone, isoniazid and Diasone and isoniazid and DHSM. The dosage of Diasone was the same as in the first series. DHSM was given in a dosage of 1 gm. twice weekly, and isoniazid in a daily dosage of 10 mg. per kilogram of body weight. The total number of patients entering was 566, and 499 completed the prescribed forty-eight weeks of therapy. The proportions showing clinical improvement or becoming worse were much the same in each of the 3 groups at each institution. All groups showed some bacteriologic improvement, but were remarkably uniform in this respect. Isoniazid, therefore, either alone or in combination with a sulfone or with DHSM, is not superior to a sulfone or to DHSM used singly in treatment of lepromatous leprosy, so far as can be determined by one year's treatment.

Thiosemicarbazones

Amithiozone (TB 1/698) has been the subject of many case reports. Dharmendra and Chatterji[15] have reviewed these and added their own experience in Calcutta. They noted a special kind of intolerance characterized by a sudden rise in temperature even after very small doses, 6 mg. to 12 mg. "Allergic dermatitis" forced withdrawal of the drug in 2 of 52 cases. They considered the clinical and bacteriologic results to be about as good as those with the sulfones. Lowe[16] has since stated that of 146 patients treated in Nigeria for periods up to twenty-one months, acute agranulocytosis developed in 4 between the third and sixth weeks of therapy. All recovered. Vegas and his associates,[17] in Venezuela, treated 70 lepromatous patients for three years, with doses varying from 100 mg. to 500 mg. daily, without serious side effects. Clinical improvement was the rule, but only 2 patients became bacteriologically negative.

In 1953 Dr. J. G. Tolentino carried out a small pilot study of amithiozone at the Eversley Childs Sanitarium as one of the Leonard Wood Memorial studies. Groups of 6, 6 and 9 lepromatous patients, all of whom had previously received either no sulfones or insignificant amounts, were matched, bacteriologically and clinically, as closely as possible. Patients of the first group were given 200 mg. of isoniazid daily and 1 gm. of DHSM three times weekly; those of the second group received 200 mg. of isoniazid and 200 mg. of DDS daily; and those of the third group were given 4 tablets daily, each containing 100 mg. of isoniazid and 12.5 mg. of amithiozone. These tablets, which were prepared by Schenley Laboratories and labeled DXP-115, were well tolerated, and treatment was continued for twenty-four weeks. Three patients of the first group, 3 of the second, and 3 of the third showed clinical improvement; none became worse. Bacteriologic changes were insignificant.

At the Sixth International Congress on Leprosy in Madrid in 1953, it was concluded that the value of amithiozone could not be definitely appraised. It was recommended that it should be used only as an alternative in patients who did not tolerate or failed to respond to sulfones.

Nonspecific Vaccine Therapy

The opinion that natural reactivity to lepromin is an indication of some degree of resistance to leprosy has led to attempts to induce reactivity in lepromatous patients by artificial means. Convit and his associates,[18] in Venezuela, and Lowe and McNulty,[19] in Nigeria, have used BCG for this purpose. A relatively small proportion of patients became lepromin positive, but there was no evidence of associated clinical or bacteriologic improvement. The effect of repeated doses of BCG as an adjuvant to DDS, and to DDS and nicotinamide, is being tested at the present time in a third series of the Leonard Wood Memorial.

Recently, Blanc et al.[20] reported, in an uncontrolled series, acquirement of reactivity to lepromin associated with clinical and bacteriologic improvement after vaccination with a killed mycobacterial vaccine prepared from *Myco. marianum,* originally isolated from a leprous nodule.

Treatment with mycobacterial vaccines or their products is not new. More than fifty years ago Deycke prepared an extract of an acid-fast microorganism cultivated from a leprous nodule. A mixture of this extract and benzyl chloride, called Nastin B, was used by a number of workers in treatment of leprosy, but the results were unsatisfactory. Repeated injections of suspensions of leprosy bacilli were given by Dharmendra, Lowe and Mukherji[21] in an unsuccessful attempt to induce reactivity to lepromin in patients with negative reactions. Tuberculin injections have been tried by several workers, with adverse results for the most part.

Cortisone and ACTH in Complications

Erythema nodosum leprosum is a common complication of lepromatous leprosy. It does not occur in the tuberculoid type. Much of the "lepra reaction" described in the older textbooks was probably erythe-

ma nodosum. There may be hundreds of subcutaneous nodules, sometimes covering the entire body but usually most frequent on the face and extremities. The overlying skin appears reddened and inflamed, and the nodules are painful on pressure. There may be high degrees of fever and painful neuritis, but sometimes the condition causes little or no inconvenience to the patient. After repeated attacks, the skin becomes thickened and brawny. Erythema nodosum is regarded as a good prognostic sign by some leprologists, but this has not been established. ACTH or cortisone will usually control the acute manifestations but the condition will recur,[22] and Lowe[23] thinks that there is grave danger of aggravating the underlying disease, particularly in patients receiving repeated courses.

Acute exacerbation of the disease, the true lepra reaction, in which old lesions of the skin and mucous membranes are aggravated and new ones appear, is a much more serious condition. High degrees of fever may persist for weeks, and death result from pneumonia or other complications.

At Carville parenteral administration of cortisone or ACTH has been used in the various acute episodes of leprosy. Doses have varied from minimal amounts for a few days to the limits consistent with safety. Cortisone has been continued for as long as ten months in an attempt to control fever, erythema nodosum and neuritis and permit continuance of sulfone therapy. Transitory improvement has usually followed; in some cases, however, these reactive conditions have persisted in spite of very high dosage. At present these hormones are being used infrequently because of toxicity and because of the possibility of aggravating the underlying bacterial infection. During recent months a few patients have been given Meticorten (synthesized by Schering Corporation), and fewer undesirable side effects have been noted.

Reaction is usually of shorter duration in the tuberculoid type than in the lepromatous and is thought by some leprologists to have a beneficial effect on the course of the infection. As in the lepromatous type, neuritis is the most distressing feature. After reaction, new contractures may develop, and old ones be accentuated. A multitude of therapeutic regimens has been employed to obtain relief. Cortisone and ACTH will control the pain temporarily; further studies are required to determine whether these hormones can limit the nerve damage and the associated deformity.

Leprosy affects the eye in two ways. Lagophthalmos occurs in both types of the disease, but more commonly in the tuberculoid. It may lead to injury of the cornea, with consequent keratitis and ulceration. The lepromatous type may affect almost any portion of the eye or adnexa. Involvement of the conjunctiva is rare. The cornea is especially vulnerable to lepromatous infiltration and ulceration. Recurring and painful attacks of iritis and iridocyclitis follow. Eventually, blindness results.

At Carville, local applications of cortisone solution have been very useful. The consulting ophthalmologist, Dr. James H. Allen, uses Cortone Acetate (synthesized by Merck) in a strength of 5 mg. per 100 cc. in distilled water. Remission of the acute process is only temporary, but the treatment appears to be equally effective on recurrence. Whether lepromatous keratitis and iridocyclitis can be kept under control indefinitely remains to be seen, but, in the meantime, pain is relieved and possession of useful sight is prolonged.

Discussion

It may be stated that by far the greatest advance in treatment of leprosy in recent years has been the introduction of the sulfones. These drugs, however, are neither curative nor bactericidal. They are of especial value in healing of lepromatous ulcers and long-continued therapy seems to assist natural processes of recovery by repressing multiplication of the bacilli. The disease apparently becomes arrested in a considerable proportion of cases. An appreciable proportion, however, relapse and may become refractory to further sulfone treatment. The Leonard Wood Memorial studies show dihydrostreptomycin to be of equivalent value to the sulfones as far as can be judged after one year of therapy. Combined treatment with a sulfone and dihydrostreptomycin offers no advantage. Except for dihydrostreptomycin, the antibiotics that have been tried are of value only in treatment of secondary infections.[24]

In the tuberculoid type the value of sulfone therapy is indicated by several reports, especially that of Lowe[12] from Nigeria, but remains to be established by controlled studies. Tuberculoid macules may become inactive without treatment of any kind, but sensory changes remain in the residual and often depigmented scars.

It should be emphasized that no method of treatment of leprosy has restored, or can be expected to restore, the anesthesia and trophic effects resulting from invasion of peripheral nerves by *Myco. leprae*. This invasion occurs early in the disease, especially in the tuberculoid type. It is also an unfortunate fact that early diagnosis is the exception; frequently, the disease goes unrecognized for several years. There is therefore urgent need for educational measures directed toward earlier recognition, as well as for discovery of a bactericidal drug.

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MEDICAL INTELLIGENCE

RICKETTSIALPOX*

Report of a Serologically Proved Case in Cleveland

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CLEVELAND

THE most recently discovered of the human rickettsial diseases, rickettsialpox, was first recognized in New York City in 1946.[1-3] Since then, cases have been reported from a relatively circumscribed area, including Boston,[4,5] Philadelphia[6] and West Hartford, Connecticut.[7] The present report extends the geographic locus of naturally occurring rickettsialpox to Cleveland.

Clinical, epidemiologic and laboratory data regarding rickettsialpox have been reported in numerous communications.[8-13] Although the course of the disease is benign, antibiotic therapy has been reported to hasten recovery.[14-16]

*From the departments of Preventive Medicine and Medicine, School of Medicine, Western Reserve University, and the University Hospitals.
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CASE REPORT

M. M., a 43-year-old married female executive in a book-publishing firm, entered University Hospitals on January 17, 1955. About 14 days previously, she had noted a small, raised, red "pimple" near the middle of the right trapezius ridge. No insect bite or trauma was recalled. Since there was no pain or itching, the lesion was not observed closely. Approximately 7 days before admission, however, the lesion was observed to be brown in color; at the time of entry the site showed merely a small, black crust.

Four days before admission, pain was felt in the right side of the neck on movement of the neck. Swelling was noted on the right side of the neck, and tender lumps were felt in this area. There was no history of sore throat. The patient was seen by her physician, who found the escharred papule on the right trapezius ridge and tender lymphadenopathy in the right posterior cervical triangle. An injection of 300,000 units of aqueous procaine penicillin was given.

The swelling and pain persisted, with slight diminution, for the next few days. On the day before entry, an intermittent temporal headache began at the time the patient awoke. She was seen again by her physician, who found fever and vesicles with surrounding zones of erythema, about 1 cm. in diameter, on the right thigh and right knee and the dorsum of the right foot.

There was no history of exposure to mice, but in October, 1954, rats were seen about the building in which the patient worked. She had resided in Cleveland continually, except for short, intrastate visits, during the 6 months before entry. In August, 1954, she had visited in Nantucket and in April, 1954, in New York City. She knew of no illness in her family or among her friends. There was no history of rheumatic fever, and she had never been told that she had heart disease.

At entry, severe headache and feverishness were the major symptoms. The patient appeared acutely ill, and her face was flushed. There were erythematous, maculopapular lesions, about 1 cm. in diameter, on the lateral aspect of the right thigh, on the right knee and on the dorsum of the right foot. These lesions bore small vesicles deep in the center of the papules. On the mid-trapezius ridge on the right, there was a black eschar, 3 mm. in diameter. Diffuse swelling was present in the area behind the right sternocleidomastoid muscle. Sufficient tenderness was encountered in this area to prevent careful palpation, but at least 3 small, tender lymph nodes could be distinguished. The neck was supple, although movement caused pain referred to the right side of the neck. No other pathologic nodes were palpable. The oropharynx was slightly red and injected. The heart was not enlarged. The cardiac rhythm was regular, and there was a Grade 2 blowing systolic murmur, heard best just to the left of the sternum in the 4th intercostal space. Liver, spleen and kidneys were not

enlarged. The remainder of the physical examination revealed only scars in the left flank (nephrectomy for cystic disease) and right breast (biopsy).

The temperature was 102.6°F., the pulse 96, and the respirations 16. The blood pressure was 102/50.

A voided specimen of urine had a specific gravity of 1.011, acid reaction and the slightest possible trace of protein, with an occasional red and white cell in the sediment. The urine benzidine reaction was positive in the slightest possible trace. The hematocrit was 41 per cent. The total white-cell count was 3500, with 45 per cent mature and 25 per cent band-form neutrophils, 22 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. Lumbar puncture (normal pressure and dynamics) revealed clear, colorless cerebrospinal fluid with 1 mononuclear cell per microliter, negative Pandy reaction and negative routine culture. Two blood cultures showed no growth after 7 days' incubation.

During the first 24 hours in the hospital, the temperature reached 103.3°F., its highest point in the illness. Headache and malaise persisted, the former requiring administration of meperidine for relief. The original skin lesions did not change. New maculopapules appeared on the left zygomatic arch and on the left side of the neck. The total white-cell count was 3200, with 60 per cent mature and 10 per cent band-form neutrophils, 16 per cent lymphocytes, 13 per cent monocytes and 1 per cent basophils. The hematocrit was 38 per cent. Voided urine again had the slightest possible trace of protein and of color with the benzidine reagent.

No new skin lesions were found after the 1st hospital day — those present gradually faded, leaving no residue. Although headache, fever, and malaise persisted on the 2d hospital day, appetite was improved. On the 3d hospital day, the temperature decreased to normal, and remained normal throughout the rest of the hospital stay. Headache subsided gradually after defervescence. On the 4th hospital day, the patient was asymptomatic, and ambulation was begun. The white-cell count at this time was 3550, with 34 per cent mature and 15 per cent band-form neutrophils, 20 per cent typical and 13 per cent atypical lymphocytes, 15 per cent monocytes and 3 per cent eosinophils. She was discharged to her home on the 6th hospital day and has remained well.

Discussion

The history and clinical appearance in this case suggested rickettsialpox. The finding of leukopenia and the course of the illness sustained this opinion. Finally, the demonstration of increased titers of complement-fixing antibody in the patient's convalescent serum (Table I) confirmed the diagnosis of rickettsialpox, since crossreaction with the antigen of Rocky Mountain spotted fever did not occur.[17]

Isolation of *Rickettsia akari,* the etiologic agent,[9] was attempted from blood, vesicle aspirate and throat washings obtained on the fifth day of illness. Albino mice and guinea pigs were inoculated with this material, and blind passage of liver and spleen from these mice was subsequently carried to other mice and guinea pigs. Embryonated hens' eggs and tissue cultures (HeLa cells) were also inoculated with this passage material. These efforts were unsuccessful.

Traps were set in the patient's home and at her place of work.* No mice or other rodents were caught. Close inspection of these premises failed to disclose arthropods characteristic of *Allodermanyssus sanguineus,* the mouse mite-vector of rickettsialpox.[10]

Blood was obtained from the patient's husband, her maid and 10 co-workers. None of these contacts gave histories of illnesses similar to that of the patient. None of the serums contained detectable amounts of complement-fixing antibody for the specific antigen of *R. akari.*

*We are indebted to Mr. E. B. Buchanan and Mr. S. J. Chorvat, of the Department of Public Health and Welfare, City of Cleveland, for their assistance in this aspect of the study.

TABLE 1. *Results of Complement-Fixation Titrations with Soluble and Specific Antigens of the Rickettsia of Rickettsialpox and Rocky Mountain Spotted Fever.**

Date of Serum	Day of Disease†	Titer for Rickettsialpox		Rocky Mountain Spotted Fever‡
		Soluble Antigen	Specific Antigen	Specific Antigen
January 17	5th	<10	<10	Not done
February 3	22d	40	80	Not done
March 10	57th	20	40	<10

*Done through kindness of Dr. Joseph E. Smadel, Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.

†Day of onset of systemic disease taken as 1st day of illness (January 13).

‡Titer expressed as reciprocal of dilution of serum; lowest dilution of serum tested, 1:10.

Summary

An illness characteristic of rickettsialpox that occurred in a resident of Cleveland is described. A rise in titer of complement-fixing antibody for *Rickettsia akari* confirmed the diagnosis, although attempts to isolate this agent were unsuccessful. The source of the infection was not discovered.

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DOCTORS AFIELD

Morton Prince

MERRILL MOORE, M.D.

BOSTON

MORTON Prince, who was born in Boston on December 21, 1854, unquestionably achieved distinction in several fields besides that of medicine: teaching, literature, the theater, politics and civic reform. His rare medical books (some of them irreplaceable) have been put together in a special collection in a room given by him to the Boston Medical Library, where many of his personal belongings, as well as his furniture and decorations, are also assembled.

After graduation from Harvard Medical School in 1879 Dr. Prince took a year of study abroad at Vienna and Strasbourg.

From 1895 - 98 he taught neurology at Harvard Medical School, and in 1902 he was appointed professor of nervous diseases at Tufts College Medical School. He was among the first to make a special plea for instruction in psychopathology at all medical schools. In 1910 he was elected president of the American Neurological Association. He lectured at the University of California, and in 1924 he delivered a series of lectures at the universities of Oxford, Cambridge, Edinburgh and London, but he himself said that the crowning result after many years of struggling for recognition at his own school (Harvard) came in 1926, three years before his death, when he was appointed associate professor in the newly created Department of Abnormal and Dynamic Psychology in Cambridge. It was during the next two years, with the assistance of Dr. Henry A. Murray, a devoted and inspired worker, that Dr. Prince succeeded in establishing a laboratory and psychologic clinic in Cambridge, which he considered to be his memorial. Dr. Prince once said that if "La Salpêtrière is a monument to Charcot, the Harvard Psychological Clinic shall be mine."

A neurologist by training and in practice, he made his first excursion as a doctor afield into literature and the theater. In 1898 a girl suffering from a type of neurosis was referred to him. Her friends regarded her as "slightly queer." In a short time, Dr. Prince discovered that within the girl, whom he called Miss Christine L. Beauchamp, three souls were struggling for mastery. These souls he called "the soul of saintliness, the soul of deviltry, and the soul of commonsense." After six years of treatment, Dr. Prince was able to eliminate the devilish "Sally" and to blend harmoniously the other elements, thus integrating her personality. In 1905 he first presented the results of this long experiment in his famous volume, *The Dissociation of a Personality*. Some of his contemporaries criticized the sensational manner in which the book was written, but Prince himself admitted that he had purposely made the style familiar to get the book read. It was the first psychologic book in this modern era of dynamic psychology to achieve almost universal public attention. Newspapers snapped it up as interesting copy; fiction writers and playwrights leaped upon the idea immediately as something wild and new. Broadway producers conservatively estimated that in the few years after its publication, at least 500 plays using "Miss Beauchamp" as their theme were rushed into their offices as fast as they could be put together. One of these plays, called "The Case of Becky," was produced by David Belasco, then the outstanding American producer, and was a hit on Broadway. Miss Frances Starr played the exacting role of the young lady with three personalities and made a name for herself in a long-run play. An interesting detail at this point is that Belasco was sued for plagiarism by a woman named Aurelia Bachman, who had written a similar play called "Estelle," but Aurelia Bachman lost her suit when Belasco proved that "Becky" was taken not from "Estelle" but directly from Dr. Prince's book.

In treating Miss Beauchamp, Dr. Prince used hypnosis and was influenced by Pierre Janet to a large extent, as well as by Gurney's experiments with hypnosis and William James's studies in automatic writing.

He was always interested in politics and public welfare. In 1901, at the request of his father, he organized the Public Franchise League, which did notable work in promoting legislation that regulated the franchises of the street and subway transportation systems and gas monopolies. In 1909 he was chairman of the Committee of One Hundred Citizens, which obtained the passing of the Boston Charter by the Legislature. He worked vigorously for its adoption by the voters when it came up on a referendum after a strenuous campaign. He later became chairman of the Boston Charter Association, which was "formed to support this Charter against the yearly attacks of politicians."

Dr. Prince was born into a relatively peaceful world twelve years after the first use of ether for general anesthesia and five years before the publication

of Darwin's *Origin of Species*, but when he was sixty years old Western Europe exploded into World War I. Even before the United States was involved in it, he became active in giving public addresses and writing for the press, and carried on organized propaganda for the cause of the Allies. He knew what the solidarity of Western Europe meant for the rest of the world. His two pamphlets, *The Creed of Deutschtum* and *The Psychology of the Kaiser*, showed penetrating insight on many levels and were extremely popular. They aroused comment everywhere. *The Psychology of the Kaiser* was translated into Japanese and also influenced the type of propaganda that the British sent over the German lines. While the war was on he dropped his medical work and went to France, where he remained during 1915 and 1916 as Boston representative of the Serbian Relations Committee. He prepared a "Message of the 500 Americans," which stated that the United States sympathized with the Allied cause, although it was officially neutral at this time. This message was answered by a token of appreciation signed by 500 French intellectuals, and Dr. Prince was honored by the French Government at a banquet in Paris at which most notables in the French Ministry were present. During the same year he was invited to Japan, where, acting on advice from Great Britain, he spoke frequently for the Allied cause. Back in the United States for a time, he wrote for the daily Boston and New York newspapers, telling what he had seen abroad. He also spoke at various clubs throughout Massachusetts on such subjects as "Prussian Militarism and Future Peace" and "The War — A Test of the German Theory of Militarism."

After the United States declared war, he offered himself for Army service, but was rejected because of age. He then attempted to form a corps of advisory physicians for work in large hospitals in this country and France, but that plan also failed. He was then appointed by Governor McCall to be head of the Massachusetts Soldiers' and Sailors' Information Bureau in Paris. It was his task to locate hundreds of soldiers who had been lost track of in transfers to and from hospitals and whose families could not locate them because the records did not keep up with the transfers. He also straightened out difficulties concerning allotments, in addition to operating a canteen and a reading room.

Because of his many experiences and contacts abroad, it was natural that he should, on his return to Boston, be appointed to many committees of reception for the various notables visiting this country. When the Serbian Mission visited Boston, Prince was chairman of the Reception Committee. In 1919 he served in the same capacity for Viscount Ishii and the Japanese Mission; he arranged an itinerary for the Japanese diplomats and was their host while they remained in Boston. In 1921 he was chairman of the State and City Commission to receive Marshal Foch, and in the same year he was chairman of the Committee to welcome General Diaz. He was awarded the Order of the Chevalier of Saint Sava, the Royal Order of the Red Cross, the Order of the White Eagle from Serbia and the Order of the Rising Sun from Japan. On September 5, 1919, he received the Cross of the Legion of Honor in the Hall of Flags in the Boston State House for his services in promoting co-operation between the United States and France during the War and in furthering the intimate relations of the two countries. Dr. Marcel Knecht, a chevalier of the Legion of Honor, at the behest of the General Commissioner, André Tardieu, conferred the decoration on Dr. Prince in the presence of state and city officials, representatives of the Army and Navy and leading men of the Boston business and professional world.

Dr. Prince was without doubt a man of strong opinions, and was not hesitant in expressing them, whether the subject was the very controversial Sacco–Vanzetti case, which he considered unfairly tried, or the cause of the League of Nations, which he strongly favored. In the matter of propaganda his enthusiasm caused him to retell Mr. Powell's stories as absolute truth, and to believe them to be true.

As those who knew him attested on many occasions, Morton Prince was a tireless physician, an uncompromising civic reformer and a strenuous, versatile participant in the social and intellectual life of his day. As a man, he might be characterized as a thinking extrovert. He saw things clearly, and he saw them whole.

Correction: In addition to the positions listed in the editorial, "Retirement of Dr. Bailey," which appeared in the December 15 issue of the *Journal*, Dr. Bailey formerly served as health commissioner of the City of Boston.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

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* * *

Blood, Plasma or Serum Values

DETERMINATION	NORMAL VALUE	MATERIAL ANALYZED	MINIMUM QUANTITY REQUIRED‡	NOTE	METHOD
			ml.		
Alpha amino nitrogen	3.0–5.5 mg. per 100 ml.	Plasma	5	Collect in heparin	Hamilton and Van Slyke: *J. Biol Chem.* **150**:231, 1943
Ammonia	40–70 microgm. per 100 ml.	Plasma		Special processing necessary	McDermott and Adams: *J. Clin. Investigation* **33**:1, 1954
Amylase	8–18 Russell units	Serum	5	—	Huggins and Russell: *Ann. Surg.* **128**:668, 1948
Ascorbic acid	0.4–1.5 mg. per 100 ml.	Blood	7	Collect in special heparin bottle immediately on admission before any food is given	Roe and Kuether: *J. Biol. Chem.* **147**:399, 1943
Barbiturate	0 Coma level: approximately 11.0 mg. per 100 ml., phenobarbital; 1.5 mg. per 100 ml., most other drugs	Serum	5	—	Goldbaum: *Anal. Chem.* **24**:1604, 1952
Bilirubin (van den Bergh test)	Direct: 0.4 mg. per 100 ml. Total: 0.7 mg. per 100 ml. Indirect is total minus direct	Serum	5	—	Malloy and Evelyn: *J. Biol. Chem.* 119:481, 1937
Bromide	0 Toxic level: 17 milliequiv. per liter	Serum	5	—	Adapted from Wuth: *J.A.M.A.* **82**:201, 1927
Bromsulfalein (BSP)	Less than 5 per cent retention	Serum	5	Inject 5 mg. per kg. of dye intravenously; draw blood 45 minutes after injection.	Goebler: *Am. J. Clin. Path.* **15**:452, 1945
Calcium	8.5–10.5 mg. per 100 ml. (Slightly higher in children)	Serum Serum	5 2	Do serum protein also Rapid method	Fiske and Logan: *J. Biol. Chem.* **93**:211, 1931 Fales: *J. Biol. Chem.* **204**: 577, 1953
Carbon dioxide content	26–28 milliequiv. per liter (20–26 milliequiv. per liter in infants)	Serum	3	Draw without stasis under oil. To calculate alveolar CO_2 and serum HCO_3 do pH also.	Van Slyke and Neill: *J. Biol. Chem.* **61**:523, 1924

*Prepared by G. Margaret Rourke, chief of Chemical Laboratory, Charles H. Du Toit, M.D., physician in charge of Chemical Laboratory and Ellen Wood, chief of Clinical Laboratory. Consultants: Philip H. Henneman, M.D., Marian W. Ropes, M.D., and William V. McDermott, M.D.

†Normal Laboratory Values. *New Eng. J. Med.* **234**:24-28, 1946, and **243**:748-753, 1950.

‡Minimum quantity refers to amount of whole blood required for a single analysis. Micromethods are available for most colorimetric methods.

For values in newborn infants refer to Smith, C.A. *The Physiology of the Newborn Infant.* 2d edition. Springfield: C C Thomas, 1951.

Determination	Normal Value	Material Analyzed	Minimum Quantity Required*	Note	Method
			ml.		
Carbon monoxide saturation	Symptoms with over 20 per cent saturation	Blood	3	Fill tube to top; tightly stopper; use anticoagulant.	Peters and Van Slyke: *Quant. Clin. Chem.* Vol. 2, p. 328, 1932
Cephalin flocculation	++ in 48 hr.	Serum	1	—	Hanger: *J. Clin. Investigation* **18**:261, 1939
Chloride	100–106 milliequiv. per liter	Serum	2	—	Wilson and Ball: *J. Biol. Chem.* **79**:221, 1928
Cholesterol	150–280 mg. per 100 ml.	Serum	2	—	Bloor: *J. Biol. Chem.* **24**: 227, 1916
Cholesterol esters	50–65 per cent of cholesterol	Serum	2	—	Bloor and Knudson: *J. Biol. Chem.* **27**:107, 1916
Cholinesterase (pseudocholinesterase)	0.5 pH units or over	Serum	1	—	Michel: *J. Lab. and Clin. Med.* **34**:1564, 1949
Congo red test	More than 60 per cent retention in the serum	Serum	6	Inject 10 ml. of 1 per cent Congo-red solution intravenously Draw blood from arm not used for injection 4 and 60 min. after injection	Unger et al.: *J. Clin. Investigation* **27**:111, 1948
Copper	Total: 130–230 microgm. per 100 ml. Free: 4 per cent of total Ceruloplasmin is total minus free	Serum	8 4	— —	Gubler et al.: *J. Biol. Chem.* **196**:209, 1952 Gubler: *J. Clin. Investigation* **32**:405, 1953
Creatine	0.3–0.6 mg. per 100 ml.	Serum	3	—	Peters: *J. Biol. Chem.* **146**: 179, 1942
Creatinine	0.7–1.7 mg. per 100 ml.	Serum	5	—	*Ibid.*
Cryoglobulins	0	Serum	10	Collect and transport at 37°C.	Barr et al.: *Ann. Int. Med.* **32**:6, 1950 (Modified)
Fibrinogen	0.15–0.30 gm. per 100 ml.	Plasma		Collect as for a prothrombin content	Cullen and Van Slyke: *J. Biol. Chem.* **41**:587, 1920 (Modified)
Fibrinolysins	0			Collect as for a prothrombin content	*Ibid.*
Glucose	Fasting: 70–100 mg. per 100 ml.	Blood	0.5	Use oxalate-fluoride bottle or microsugar tubes	Folin: *New Eng. J. Med.* **206**:727, 1932
Hemoglobin	Males: 13–16 gm. per 100 ml. Females: 12–14 gm. per 100 ml.	Blood	0.02	—	Evelyn: *J. Biol. Chem.* **115**:63, 1936
Electrophoresis for hemoglobin C and S	0	Blood	5	Use oxalated blood	Singer: *Am. J. Med.* **18**: 633, 1955
Alkali resistance for fetal hemoglobin	Less than 2 per cent resistance	Blood	5	Use oxalated blood	*Ibid.*
Hemoglobins, met- and sulf-	0	Blood	5	Use heparinized blood; deliver immediately.	Michel and Harris: *J. Lab. and Clin. Med.* **25**:445, 1940
Iodine (Protein bound or hormonal)	3.5–8.0 microgm. per 100 ml.	Serum	12	Avoid iodide therapy, x-ray contrast media, iodine on skin	Barker: *J. Biol. Chem.* **173**:715, 1948
Iron	50-200 microgm. per 100 ml. (higher in males than in females)	Serum	10	—	Barkan and Walker: *J. Biol. Chem.* **135**:37, 1940
Iron binding capacity	Serum iron equals 20-50 per cent of capacity	Serum	12 (Includes serum iron)	Draw fresh serum. Patient must be fasting	Cartwright and Wintrobe: *J. Clin. Investigation* **28**:86, 1948
Lactic acid	6-16 mg. per 100 ml.	Blood	2	Use special bottles with iodoacetate; draw without stasis. Patient must be fasting and at complete rest	Barker and Summerson: *J. Biol. Chem.* **138**:535, 1941

*Minimum quantity refers to amount of whole blood required for a single analysis.

Determination	Normal Value		Material Analyzed	Minimum Quantity Required*	Note	Method
				ml.		
Lipase	Under 2 units		Serum	5	—	Comfort and Osterberg: *J. Lab. & Clin. Med.* **20**: 271, 1934
Lipid partition:	*Mg. per 100 ml.*	*As fatty acid milliequiv. per liter*	Blood	20	Done on fasting serum	
Cholesterol	150-280					See above
Cholesterol esters	50-65 per cent of cholesterol	1.75-4.30				
Phospholipids as Phosphorus	220-400 9-16	5.00-9.00				Fiske and Subbarrow: *J. Biol. Chem.* **66**:2, 1925
Total fatty acids	190-420	6.9-15.2				Stoddard and Drury: *J. Biol. Chem.* **84**:741, 1929
Neutral fat	0-200	0-7.0			Calculated from above values	
Magnesium	1.5-2.5 milliequiv. per liter		Serum	5	—	Garner: *Biochem. J.* **40**: 828, 1946
Nonprotein nitrogen	15-35 mg. per 100 ml.		Serum	3	—	Folin: *Lab. Manual Biol. Chem.* Fifth ed. p. 265, 1934
Osmotic pressure	285-295 milliosmols per liter		Serum	5	In cases of uremia NPN should be done to apply a correction	Crawford and Nicosia: *J. Lab. & Clin. Med.* **40**: 907, 1952
Oxygen saturation (arterial)	96-100 per cent			10	Use special syringe with heparin	Van Slyke and Neill: *J. Biol. Chem.* **61**:523, 1924
pH	7.35-7.45		Serum	2	Collect under oil without stasis; pack in ice; deliver immediately.	Hastings and Sendroy: *J. Biol. Chem.* **61**:695, 1924
			Blood	5	Collect same as for oxygen; deliver immediately. Preferred for evaluation of respiratory acidosis	pH meter
Phosphatase, acid	0.5-2.0 units, total 0.0-0.6 units, prostatic		Serum	10	Must always be drawn just prior to analysis	Fishman and Lerner: *J. Biol. Chem.* **200**:89, 1953
Phosphatase, alkaline	2.0-4.5 units (infants to 14 units; adolescents to 5 units).		Serum	3		Bodansky: *J. Biol. Chem.* **101**:93, 1933
Phosphorus, inorganic (Phosphate)	3.0-4.5 mg. per 100 ml. (as phosphorus) (Infants in first year: up to 6.0 mg. per 100 ml.)		Serum	1	Of value only if patient is fasting	Fiske and Subbarrow: *J. Biol. Chem.* **66**:375, 1925
Potassium	3.5-5.0 milliequiv. per liter		Serum	2	Must not stand on cells more than 1 hr. (Flamephotometer)	Adapted from Berry, Chappell and Barnes: *Indust. & Engin. Chem.* **18**:19, 1946
Protein:						
Total	6.0-8.0 gm. per 100 ml.		Serum	1 (micro)	Preferably fasting; avoid BSP dye.	Lowry and Hastings: *J. Biol. Chem.* **143**:257, 1947
			Serum	5 (macro)		Cornall: *J. Biol. Chem.* **177**:751, 1949
Albumin	4.5-5.5 gm. per 100 ml.		Serum	5		Howe: *J. Biol. Chem.* **49**: 109, 1921; Cornall: *J. Biol. Chem.* **177**:751, 1949
Globulin	1.5-3.0 gm. per 100 ml.				Globulin calculated by difference	
Protein: Electrophoresis of (paper)			Serum	1	—	Kunkel and Tiselius: *J. Gen. Physiol.* **35**:89, 1951

*Minimum quantity refers to amount of whole blood required for a single analysis.

Determination	Normal Value	Material Analyzed	Minimum Quantity Required*	Note	Method
	Percentage of total protein		*ml.*		
Albumin	45-55				
Globulin:					
Alpha-1	5-8				
Alpha-2	8-13				
Beta	11-17				
Gamma	15-25				
Prothrombin content	100 per cent of control plasma	Plasma	2	Use special oxalate tube; collect rapidly; send to laboratory at once.	Quick: *J.A.M.A.* **110**: 1658, 1938
Prothrombin consumption	Over 85 per cent prothrombin consumed in 1 hr.	Citrated plasma and serum	2 (citrated) 3 (clotted blood)	Collect in special citrate tube and clean test tube; note time of drawing; take immediately to laboratory.	Stephanini and Crosby: *Blood* **5**:964, 1950
Pyruvic acid	1.0-2.0 mg. per 100 ml.	Plasma	2	Use special iodoacetate tube; avoid stasis. Patient must be fasting and at complete rest	Friedemann and Haugen: *J. Biol. Chem.* **147**:415, 1943
Salicylate:		Plasma	5	Collect in heparin or oxalate	Keller: *Am. J. Clin. Path.* **17**:415, 1947
Therapeutic	20-25 per 100 ml.				
Toxic	over 30 mg. per 100 ml. for aspirin (5 mg. or higher if sodium salicylate is the drug)				
Sodium	136-145 milliequiv. per liter	Serum	3	Flamephotometer	Adapted from Berry, Chappell and Barnes: *Indust. & Engin. Chem.* **18**:19, 1946
Sulfonamide	0	Either blood or serum	2	—	Bratton and Marshall: *J. Biol. Chem.* **128**:537, 1939
Thymol					
Flocculation	Up to + in 24 hr.	Serum	1	—	McLagen: *Nature* **154**: 670, 1944
Turbidity	0-4 units	Serum	1		*Ibid.*
Transaminase	10-40 units	Serum	1	—	Karmen et al.: *J. Clin. Investigation* **32**:126, 1955
Urea	12-25 mg. per 100 ml. (as urea N) 25-52 mg. per 100 ml. (as urea)	Serum	3	—	Van Slyke: *J. Biol. Chem.* **73**:695, 1927
Uric acid	3.0-6.0 mg. per 100 ml.	Serum	3	—	Folin: *J. Biol. Chem.* **101**: 111, 1933
Vitamin A and Carotenoids					
Total	1-3 units per ml.	Serum	5	Use same sample	Josephs: *Bull. Johns Hopkins Hosp.* **65**:112, 1939
Vitamin A	0.3-1 unit per ml.	Serum			
Vitamin A Tolerance test	Normal rise to twice fasting level in 3 to 5 hr.		5	Children: 0.1 ml. oleopercomorphum per lb. body weight Adults: 200,000 units vitamin A Take 5-ml. samples with the patient fasting, and 3, 5 and 7 hr. later. May eat foods of low-fat content during test	May et al.: *Am. J. Dis. Child.* **59**:1167, 1940
Volume of blood	8.5-9 per cent of body weight in kg.	Sera	4 each	Inject exactly 10 ml. of 0.1 per cent Evans blue in saline intravenously; draw blood before and 5 and 10 minutes after injection.	Gregerson and Stewart: *Am. J. Physiol.* **125**:142, 1939
		Blood	2	Send blood for hematocrit; use double oxalate tube.	

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Urine Values

Determination	Normal Value	Minimum Quantity Required	Note	Method
Alpha amino nitrogen	64-199 mg. per diem. Not over 1.5 per cent of total nitrogen	24-hr. specimen	Preserve with thymol; refrigerate.	Same as for blood
Ammonia	20-70 milliequiv. per liter	24-hr. specimen	Collect under toluol; refrigerate.	Van Slyke and Cullen: *J. Biol. Chem.* **24**:117, 1916
Calcium	Under 150 mg. per diem	24-hr. specimen	Collect in special bottle with HCL	Same as for serum
Corproporphyrin	50-250 microgm. per diem	24-hr. specimen	Collect with 5 gm. of sodium carbonate	Schwartz: *J. Lab. & Clin. Med.* **37**:843, 1951
Creatine	Under 100 mg. per day or less than 6 per cent of creatinine In pregnancy up to 12 per cent. Children under 1 year: may equal creatinine; older children: up to 30 per cent of value of creatinine.	24-hr. specimen	Preserve with toluol	Folin: *Lab. Manual Biol. Chem.* 5th ed., p. 163, 1933
Creatinine	15-25 mg. per kg. of body weight	24-hr specimen	Preserve with toluol	*Ibid.*
Follicle stimulating hormone	Before puberty: less than 6.5 mouse units; after puberty: 6.5-52 units. After menopause: 96-100 units	24-hr. specimen	Done by "too little" method Done by "too much" method	Klinefelter et al.: *J. Clin. Endocrinol.* **3**:529, 1943
17-ketosteroids	Age Males Females 10 1-4 mg. 1-4 mg. 20 6-21 4-16 30 8-26 4-14 50 5-18 3-9 70 2-10 1-7	2 successive overnight 12-hr. specimens	—	per Vestergaad: *Acta Endocrinol.* **13**:241, 1953 Normal values taken from Hamburger: *Acta Endocrinol.* **1**:19, 1948
Lead	To 0.08 microgm. per ml. or 120 microgm. total for adult	24-hr. specimen	—	Bessman and Layne: *J. Lab. & Clin. Med.* **45**: 159, 1955
Phenolsulfonphthalein (PSP)	At least 25 per cent by 15 min., 40 per cent by 30 min., 60 per cent by 120 min.	Total output of urine collected 15, 30 and 120 minutes after injection	Inject 1 ml. (6 mg.) intravenously	Chapman: *New Eng. J. Med.* **214**:16, 1936
Porphobilinogen	0	10 ml.	Freshly voided specimen	Watson and Schwartz: *Proc. Soc. Exper. Biol. & Med.* **47**:393, 1941
Protein:				
Quantitative	0	24-hr. specimen	Preserve with toluol; refrigerate.	Hawk, Oser and Summerson: *Pract. Physiol. Chem.* 12th ed., p. 868, 1948
Bence–Jones	0	50 ml.	Fresh urine specimen	Jacobson and Milner: *Am. J. Clin. Path.* **14**:138, 1944
Electrophoresis of	0	50 ml.	Fresh urine specimen. Done for suspicion of multiple myeloma. Do serum simultaneously	See serum proteins
Sugar:				
Quantitative	0	Done on 24-hr. or divided 24-hr. specimens	Collect under toluol; refrigerate.	Somogyi: *J. Lab. & Clin. Med.* **26**:1220, 1941
Nonglucose reducing substance	0	50 ml.	Use fresh specimen without preservative	—
Urea Clearance	75-125 per cent of normal	Serum and urine 6 cc. blood; two exactly timed 1-hr. samples of urine	—	Peters and Van Slyke: *Quant. Clin. Chem.* Vol. 2 (Methods), p. 564, 1932
Urobilinogen	Up to 1.0 Ehrlich units	2-hr. sample (1-3 p.m.)	—	Watson et al.: *Am. J. Clin. Path.* **15**:605, 1944

Hematologic Values

Determination	Normal Value	Minimum Quantity Required*	Note	Method
		ml.		
Bleeding time:				
Method I	Below 4½ minutes	—	—	Dukes: *J.A.M.A.* 55:1185, 1910
Method II	Below 6½ minutes	—	—	Jacobson: *Arch. Int. Med.* **92**:471, 1953
Clotting time	Below 20 minutes 4th tube	12	Draw at bedside; use 5 tubes.	Lee and White: in Todd and Sanford: *Clin. Diag. by Lab. Methods.* 10th ed., p. 199, 1943
Erythrocyte sedimentation rate				
Method I	Less than 0.4 mm. per min. corrected for hematocrit	5	Use heparin as anticoagulant	Rourke and Ernstene: *J. Clin. Investigation* **8**: 545, 1930
Method II (Screening purposes)	Less than 20 mm. in 1 hr.	5	Use double oxalate or sequestrene tube	Similar to Wintrobe and Landsberg: *Am. J. M. Sc.* **189**: 102, 1935 (Differs in use of 4-mm. tube)
Osmotic fragility of red cells	Increased if hemolysis occurs in over 0.5 per cent NaCl; decreased if hemolysis is incomplete in 0.3 per cent NaCl.	5	Use double oxalate tube	Hunter: *J. Clin. Investigation* **19**:691, 1940
L. E. (lupus erythematosus) preparation:				
Method I	Normally negative	5	Use blood in heparin	Hargreaves et al.: *Proc. Staff Meet., Mayo Clin.* **24**:234, 1949
Method II		5	Use defibrinated blood Method II more sensitive but positive results in diseases other than lupus may be more frequent	Barnes et al.: *J. Invest. Dermat.* **14**:397, 1950
Platelet count	250,000 to 450,000	5	Use special sequestrene tube	Brecher et al.: *Am. J. Clin. Path.* **23**:15, 1953
Hematocrit	Males: 42-50 mm. females: 40-48 mm.	2	Use double oxalate tube	Wintrobe: *Clin. Hematol.* 3rd. ed., pp. 328-334, 1946
Hemoglobin	Males: 13-16 gm. per 100 ml. females: 12-14 gm. per 100 ml.	0.05	—	See above
Wintrobe indices: Mean corpuscular volume (MCV)	80-94 cu. microns		Wintrobe indices depend on meticulous performance of basic measurements	(Hematocrit x 10) ÷ red cells (in millions)
Mean corpuscular hemoglobin (MCH)	27-32 micromicrogm.			(Gm. of hemoglobin x 10) ÷ red cells (in millions)
Mean corpuscular hemoglobin concentration (MCHC)	33-38 per cent			(Gm. of hemoglobin x 10) ÷ hematocrit

*Minimum quantity refers to amount of whole blood required for a single analysis.

Cerebrospinal-Fluid Values

Determination	Normal Value	Minimum Quantity Required	Note	Method
		ml.		
Initial pressure	70-180 mm. of water	—	—	—
Cell count	0-5 mononuclear cells	0.5	—	—
Chloride	120-130 milliequiv. per liter	0.5	20 milliequiv. per liter higher than serum; obtain serum for comparison.	Same as that for serum (see above)
Protein:				
Lumbar	15-45 mg. per 100 ml.	1	—	Adapted from Ayer et al.: *Arch. Neurol. & Psychiat.* **26**:1038, 1931
Cisternal	15-25 mg. per 100 ml.			
Ventricular	5-15 mg. per 100 ml.			
Glucose	50-75 mg. per 100 ml.	0.1	20 mg. less than blood; do blood for comparison.	Same as that for blood
Colloidal gold	0000000000	0.1	—	Wuth and Faupel: *Bull. Johns Hopkins Hosp.* **40**:297, 1927

Miscellaneous Values

Determination	Normal Value	Minimum Quantity Required	Note	Method
Duodenal drainage:				
pH	5.5-7.5	1 drop		
Amylase	Over 1,200 Russell units	1 ml.	pH should be in proper range with minimum amount of gastric juice present	Same as for serum
Trypsin	Digestion of gelatin in 1 to 50 dilution or higher. Formerly reported as percentage of normal based on ideally collected control specimens, which on the average digested in 1 to 1000 dilution. Values from 35 to 160 per cent normal are encountered in patients without pancreatic disease	1 ml.	*Ibid.*	Anderson and Early: *Am. J. Dis. Child.* **63**:891, 1942
Viscosity	3 min. or under	4 ml.	Run ice cold in 34-second viscosometer	
Stool fat	Less than 5 gm. in 24 hr. or less than 4 per cent of fat intake in a three-day period determined by carmine marker	24-hr. or 3-day specimen		Van de Kramer et al.: *J. Biol. Chem.* **177**:374, 1949
Stool nitrogen	Less than 2 gm. a day or 10 per cent of urinary nitrogen	24-hr. or 3-day specimen		Peters and Van Slyke: *Quant. Clin. Chem.* Vol. 2 (Methods), p. 353, 1932

CASE 42011

Presentation of Case

A fifty-nine-year-old Greek-born woman was admitted to the hospital because of jaundice and disorientation.

Ten days previously there was an acute onset of nausea, vomiting, fever and chills followed shortly by painless jaundice. About four days before entry the patient became disoriented and bedridden. Because of anorexia and vomiting she had taken only fluids. Shortness of breath was noted three days before admission along with increasing weakness. She had not taken Thorazine or methyl testosterone. There was no contact with anyone who was jaundiced. Rats were known to be present in the patient's house. Three hundred thousand units of penicillin had been given intramuscularly about a week before admission.

She had had malaria thirty-six years and a groin abscess twenty years previously. There was no history of alcoholism.

Physical examination showed an acutely ill, obese, jaundiced, disoriented woman with a uremic frost about the nose and a fetid breath. The tongue was coated with dried blood. Increased dullness and wet rales were noted over the right-lung field. Dry rales were heard at the left base. The heart was slightly enlarged to the left. The abdomen was markedly obese, with tenderness in the right upper quadrant. Liver dullness was percussed 5 cm. below the right costal margin. The spleen was not palpable. Peristalsis was diminished. There was ++ edema of the legs.

The temperature was 101°F., the pulse 102, and the respirations 40. The blood pressure was 90 systolic, 55 diastolic.

The urine, which was dark amber and cloudy, had a specific gravity of 1.014, and gave a + test for albumin, a negative sugar reaction and a ++++ test for bile; the sediment showed numerous bacilli and a rare white cell per high-power field. Examination of the blood revealed a hemoglobin of 12.1 gm. per 100 ml. and a white-cell count of 13,600, with 82 per cent neutrophils. The platelets and red cells appeared normal. The nonprotein nitrogen was 215 mg., the total protein 6.5 gm., with an albumin-globulin ratio of 1.2, and the bilirubin 19.6 mg. direct and 24.3 mg. total per 100 ml., the thymol turbidity 2.5 units, and the serum amylase 11 Russell units. The prothrombin content was 67 per cent of normal, the cephalin flocculation ++++ in twenty-four hours, and the thymol flocculation negative. The sodium was 118 milliequiv., the chloride 77 milliequiv., the potassium 7.6 milliequiv. and the carbon dioxide 13 milliequiv. per liter. Serum pH was 7.45. Stools were clay colored and gave a slightly positive guaiac test. An electrocardiogram revealed prominent P waves, but otherwise the tracing was within normal limits. An x-ray film of the chest demonstrated what appeared to be infiltration throughout the right-lower-lung field. On gastric aspiration a small amount of slightly guaiac-positive material was obtained.

Therapy included intravenous infusions of dextrose and saline as well as Hykinone, Cedilanid and antibiotics. The patient failed to improve, becoming unresponsive, and died on the second hospital day. Terminally, the temperature rose to 104.2°F.

Differential Diagnosis

Dr. Daniel S. Ellis*: Obviously, this patient was desperately ill when she was admitted to the hospital and did not live long enough for the usual diagnostic procedures. The physician, I am sure, had to decide on relatively little evidence what to do for her. It seems obvious to me that she had an infection of some kind. Before discussing the possibilities, I should like to see the x-ray films.

Dr. C. C. Wang: We have a set of unsatisfactory examinations. The examination of the chest consists of only one film, taken in the supine position, which demonstrates what appears to be an area of infiltration in the right-lower-lung field. I cannot be sure of the outline of the right leaf of the diaphragm. The remaining lung fields appear to be clear. The heart is not unusual in size.

Dr. Ellis: Do you think the old calcification is significant?

Dr. Wang: I think the calcification overlying the right apex is in the cartilage of the ribs.

Dr. Ellis: Is the infiltration of which you spoke consistent with pneumonia?

Dr. Wang: It is an area of consolidation; it could be pneumonia or an infarct. The abdominal film is grossly inadequate, but does show a fair amount of gas in the small and large bowel. The cecum is somewhat dilated. There is no gross obstruction of the small bowel that I can see. The stomach contains some gas, and if this shadow represents the tip of the spleen, the spleen is enlarged.

Dr. Ellis: "If it does!" Does it?

Dr. Wang: I do not know; I cannot be sure.

Dr. Ellis: Can you tell me about where the lower edge of the liver is? The examiner said that he percussed it; he did not say he felt it.

Dr. Wang: It is not very low.

Dr. Ellis: In addition to the evidence for an overwhelming infection manifested by acute febrile onset with chills and fever, leukocytosis and rapidly downhill course, one is struck by the unequivocal evidence of uremia. Uremic frost around a patient's mouth, which I do not see too commonly, denotes a severe degree of uremia to me; that was borne out by the nonprotein nitrogen of 215 mg. per 100 ml.

*Assistant physician, Massachusetts General Hospital.

There seems to be no doubt that the patient had some decompensation of the kidneys. One wonders whether it was on an extrarenal basis or the result of parenchymal damage to the kidney itself. I am bothered by the fact that there were no more abnormal findings in the urinary sediment. I assume that only one urinalysis was done, but even so she should have had more than a + test for albumin just on the basis of the febrile illness. In addition to the failure to handle the nitrogenous waste there was severe decompensation of the liver, manifested by jaundice, by the ++++ cephalin flocculation and possibly by the increased bleeding tendency, with blood in the mouth and in the gastrointestinal tract. The bleeding, of course, could occur in terminal uremic states as well.

With respect to the lung, one wonders whether or not there was a pneumonia. My opinion is that the process in the lung was associated with the primary disease and was not itself the primary disease. One might raise the question of whether the jaundice was associated with a massive pulmonary infarct. Although this is frequent, particularly in the presence of congestive heart failure, it does not commonly produce a positive cephalin flocculation unless there is coexisting hepatic disease. Therefore, I think that I shall say that the process in the lung was a hypostatic pneumonia secondary to the critical state of the patient, although I cannot exclude the possibility of a pulmonary infarct.

What infections may be ruled in or out on the basis of the information available? There is nothing in the protocol that does not fit the picture of acute fulminating Weil's disease. This patient had a ten-day history; an acute onset, with chills and fever; and jaundice associated with uremia and with gastrointestinal bleeding; and finally died. Weil's disease usually is not fatal; the best statistics that I could find indicated that the mortality is 5 per cent or less. That is a rare disease, and is rarely seen in this hospital. I have read about it ever since I went to medical school, but I have never seen a case. I am not paying too much attention to the "red herring" that is thrown in almost every protocol of a patient with jaundice and fever — namely, that rats were in her home; however, the picture is consistent with Weil's disease.

The other conditions that one has to consider are acute cholangitis, gallstones and possibly pancreatitis, even though the amylase was normal. Nothing in the picture except the lack of a past history of biliary colic rules out an acute cholangitis, associated with an inflammatory process in the gall bladder with or without stones. Chills and fever and the palpable liver on the basis of an obstructive type of jaundice fit in. The examiners did not feel the spleen, and Dr. Wang cannot say whether or not he sees the spleen, so I shall assume that it probably was not enlarged. The only reason that it is difficult for me to hold to the diagnosis of cholangitis and infection in the biliary tract is the fact that I have to postulate an extra disease to explain the renal difficulties and the uremia. One wonders whether or not the uremia was extrarenal on the basis of marked dehydration from vomiting. That is certainly a possibility and may be the reason for the relatively few abnormal findings in the urinary sediment.

The other possibility, although I think it is unlikely, is widespread neoplastic disease involving the liver in the terminal stage and possibly the lungs. Again, the renal picture could be on the basis of a coincidental chronic nephritis or dehydration. Perhaps Dr. Lerman might express an opinion about whether or not the blood chemical levels and the urinary findings are consistent with dehydration rather than primary renal disease.

DR. JACOB LERMAN: I was going to ask you the same question. There is something peculiar about a carbon dioxide of 13 milliequiv. per liter and a pH of 7.45 along with a low blood sodium and chloride. The patient may have been overbreathing.

DR. ELLIS: Having mentioned the various possibilities, I think if I made my decision on the findings listed in the protocol I should say that this patient died of Weil's disease. On the law of averages, however, the more usual and more likely possibility is that she had an acute ascending cholangitis; cholecystitis, with secondary dehydration; uremia on the basis of the dehydration; and possibly some impairment of renal reserve on the basis of old nephrosclerosis. Frankly, I am torn between the two diagnoses, but on the reasoning that I have just stated, I shall choose infection in the biliary tract, with a combination of infection in the biliary tract, dehydration and uremia, and place Weil's disease as a second choice.

DR. N. JOEL EHRENKRANZ: I think it would be most unusual for Weil's disease to produce this amount of renal involvement without any evidence of hematuria. As far as other infection is concerned, the possibility of jaundice due to pylephlebitis might be considered.

DR. STEPHEN KRANE: There is nothing in the protocol that would not be consistent with the ingestion of some toxin like carbon tetrachloride.

DR. AUSTIN L. VICKERY: That was carefully investigated.

DR. ELLIS: That would not fit well with the acute onset of chills and fever.

DR. PETER BALLY: The urinalysis was done on a specimen obtained on admission. Thereafter, she went into complete renal shutdown and no further specimen could be obtained.

The patient had received 3000 ml. of 5 per cent glucose in water before she came up to the ward. Hence, it is possible that the low electrolyte values represented more extracellular dilution. Therapy from then on was mainly aimed at correction of the

hyperpotassemia, which appeared to be due to renal shutdown and was probably purely extracellular since there were no typical electrocardiographic changes. Partial correction could be obtained with concentrated glucose and insulin as well as cation-exchange resin through gastric washing. Sodium was replaced by concentrated saline and lactate but renal function never returned.

DR. VICKERY: In the record I noted that you had interrogated the family very closely about carbon tetrachloride and other toxic agents; but no history of such exposure was obtained. However, I cannot help mentioning the remarks of two house-staff members regarding the reliability of the informant here. One physician's comment was that the patient was "unreliable and disoriented" and that the family was "unreliable and unintelligent." The other physician's comment was that everybody was "totally unreliable."

DR. MARSHALL K. BARTLETT: Dr. Ellis, did the relatively high serum bilirubin help you in any way?

DR. ELLIS: I think that fits in with the ++++ cephalin flocculation, and I should prefer to say that I was dealing with a diffuse parenchymal liver disease such as hepatitis or severe Weil's disease in explaining that, rather than the diagnosis that I made my first choice, but we do see patients with severe obstructive jaundice and a ++++ cephalin flocculation. I accept it as something that does not usually occur with short-standing cholangitis, but I think there was enough liver damage to account for it. Dr. Vickery told me a few days ago that the patient's transaminase was 100 units. That was further evidence of tissue destruction somewhere, but it did not make me change my mind. I am sure that she had a "sick" liver and "sick" kidneys, but I think the "sick" kidneys were secondary to the dehydration and the "sick" liver can be explained on the basis of one of the two possibilities that I mentioned. I do not think this was hepatitis or cirrhosis.

CLINICAL DIAGNOSES

Acute renal failure.
Acute necrosis of liver.
Pneumonia.
Congestive heart failure.

DR. DANIEL S. ELLIS'S DIAGNOSES

Ascending cholangitis and cholecystitis.
Uremia as result of dehydration.

ANATOMICAL DIAGNOSES

Choledocholithiasis, chronic, extrahepatic and intrahepatic, with obstruction of ampulla of Vater.
Cholangitis, acute, ascending.
Hepatic abscesses, acute, multiple.
Cholecystitis, chronic.
Cholelithiasis.
Choledochitis, chronic.
Bile nephrosis.
(Septicemia), coliform bacilli.
Acute splenitis, with splenomegaly.

PATHOLOGICAL DISCUSSION

DR. VICKERY: The liver was enlarged to roughly double the normal weight at the time of autopsy, weighing 3200 gm. Its surface was studded with fluctuant blebs, which proved to be abscess cavities. Section through the liver showed similar irregularly outlined abscesses scattered throughout the parenchyma but concentrated in greatest number around the gall-bladder bed. The abscesses measured up to 2.5 cm. in diameter and were filled with thick, cloudy, green fluid, which contained gas bubbles. Further examination of the liver and extrahepatic biliary tree disclosed more rather startling findings. The gall bladder, cystic duct and common bile duct were all filled with white, faceted stones, averaging about 1 cm. in diameter (Fig. 1). A particularly large

FIGURE 1. *Portion of the Liver, Showing Intrahepatic and Extrahepatic Gallstones.*
Arrow labeled A *points to stones in the gall bladder, arrow labeled* B *to stones in the common duct, and arrow labeled* C *to stones in the intrahepatic bile duct.*

calculus (1.5 cm. in diameter) was impacted at the ampulla of Vater. The intrahepatic biliary channels were also dilated, and the larger ones contained numerous small gallstones. The gall-bladder wall was thickened and fibrotic. The acuteness of this disease, I believe, is attested to by the absence of any evidence of chronic inflammatory or fibrotic reaction in the liver. These are acute abscesses without any type of fibroblastic activity, all of which seems to be consistent with a relatively short duration, as Dr. Ellis correctly predicted. The spleen was enlarged; it weighed 510 gm. and was mushy, probably on the basis of the septicemia, which the patient certainly must have had. Post-mortem cultures of liver, kidney and bile all grew out coliform bacilli.

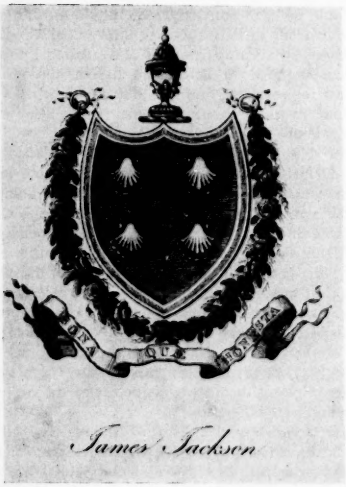
The lungs were merely very congested and edematous; no bronchopneumonia was found.

In retrospect, it seems that she had had chronic gall-bladder disease over a period of years, for the gall bladder was thickened and its wall was fibrotic. Undoubtedly, she had had calculi for a long time, not only in the gall bladder but also in the common duct, for the latter was dilated and its wall was thickened. The patient probably then had been forming stones for years, not only in the gall bladder, but also in the biliary radicles within the liver itself, a condition that had apparently been asymptomatic — that is, within the limits of the history reliability.

DR. ELLIS: What were the kidneys like, Dr. Vickery?

DR. VICKERY: The kidneys were swollen and weighed 490 gm. together. We expected to see acute pyelonephritis on the basis of the septicemia, but the kidneys did not show any abscesses whatsoever. Instead, we found the histologic picture of bile nephrosis or cholemic nephrosis, which is quite similar to that seen in hemoglobinuric nephrosis but with bile-pigment casts. This condition, in addition to the state of dehydration, which Dr. Ellis commented on, probably accounted for the elevated nonprotein nitrogen. In any event there did not seem to be any significant chronic renal disease or anything of an infectious nature to contribute to the terminal uremia.

DR. BALLY: Blood had been taken for agglutination studies for leptospirosis; the results, received after the patient's death, were negative.



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RESCUING MEDICAL EDUCATION

IN late November the Commonwealth Fund announced the outright gift of $7,150,000 from its capital funds to 10 of the medical schools of the country. The fact of the gift is no longer news, but like other shots heard around the world its reverberations may well awaken various agencies to the present financially impoverished state of medical education, and the part that they may play in its alleviation.

The numerical supply of doctors in this country will not fail conspicuously so long as the law of supply and demand remains on the economic statute book. The existing 81 four-year schools of medicine will be augmented by 4 next fall, and the present enrollment of 28,000 students represents an increase of 6000 in a decade. The number of applicants has fallen off, nevertheless, and already the plane of scholarship in medicine has shown signs of declining to the point where it is causing just concern at discriminating levels. At other levels the distinction between quality and quantity has remained obscure, and medical education has been in some danger of deteriorating into mere technical training.

Admittedly, considerable sums of money from private and public sources have come to medical institutions the country over. Rarely has it come in the most needed form, however, without limitation on its uses, but too often in fancy packages restricted largely to specific research projects. Such gifts, acceptable as they are, may require still further allocations from an institution's unrestricted funds by absorbing that proportion of the available income that is required to house and harbor the project. Grants for research, in order to avoid the risk of becoming financial embarrassments, need also to be endowed.

The National Fund for Medical Education has raised, largely from industry and from physicians themselves, an average sum of $2,500,000 annually in the seven years of its existence, but to the Commonwealth Fund goes the distinction of being the first large foundation to see the whole picture in its true perspective. To play still further with the simile of a shot heard 'round the world, one may think of the Commonwealth Fund as having become, in the words of Dean Berry of Harvard Medical School, the first of the great philanthropic agencies to break the sound barrier that has prevented a true appreciation of the plight of medical education, and the necessity of doing something about it.

The Commonwealth Fund's Thanksgiving gift is significant in various ways. It represents an allocation of principal, in addition to the $2,000,000 that had already been given from income in the fiscal year; it is unrestricted, to make it most effective in strengthening educational programs, and, perhaps most important, it points up the urgency of the present need and the great financial handicap that medical education is trying to overcome.

It may be asked how 10 schools from a list of 81 were selected to be the recipients of this great distribution of funds. Actually, the elimination of those that are supported to any degree by tax money narrowed the list to 27; the 10 university medical schools that were then chosen—Chicago, Columbia, Cornell, Emory, Harvard, New York University, Southern California, Tulane, Western Reserve and Yale—were picked on the basis of strong support by their own faculties, students and alumni and their creative programs in medical education. In this way the trustees of the Fund believe that they are carrying out the design of Mrs. Stephen V. Harkness, its founder, "To do something for the welfare of mankind."

Not only do those responsible for the Fund hope that by this action similar unrestricted giving from other sources will be inspired, but they are themselves continuing the study of other medical schools in line with their announced policy of enabling schools to make faster progress in this critical period of reappraisal of the structure of education.

To the extent that private sources will support medical education, tax support will be unnecessary. Beyond that point the burden must eventually fall upon the public through its government, most equitably in the form of intelligent support of a broad and far-seeing health program, not in the form of multiple Christmas-wrapped packages for worthy but restricted purposes.

This original distribution of funds may seem at first like a fulfillment of the proverb that to him that hath shall be given; rather, it may be taken as a reminder that divine help comes to those who have themselves taken some initiative in the matter. On this basis there is little question that medical education in general is looking up. That all education and all mankind will share in this renascence is borne out by the more recently announced magnificent pre-Christmas gift of the Ford Foundation. This colossal nationwide act of philanthropy opens still another chapter in the private support of higher education and may indeed point toward a different and more satisfactory ending to the story than that of unlimited federal aid.

CORTISONE, ACTH AND INFECTION

Most practicing physicians, in reading the general medical literature, have probably become convinced that the adrenocortical hormones represent life-saving measures in the management of serious or fulminating infections. Perhaps the most constant advocate of their use in the widest range of infectious diseases has been Kinsell, whose most recent paper[1] is based on experience with combined hormonal and antibiotic therapy in more than 300 patients with severe systemic infections. His conclusion is that such therapy, when properly administered, may result in lessened morbidity and mortality, whereas its injudicious use may have precisely the opposite effect. A number of principles are evoked to explain the good effects, but the conclusion must be accepted for what it really is—namely, an empirical deduction from clinical observations that lacks the force of conviction because of the absence of acceptable controls. The same statement may be made of the otherwise convincing clinical observations that have led some highly competent investigators in the field of infectious diseases to recommend such therapy in typhoid and typhus fevers, brucellosis and meningococcemias and in certain cases of tuberculosis, particularly those of the meningeal form.

On the other hand, cautious reserve has been advocated by other workers whose clinical experiences have been tempered by the results of controlled observations made in experimental infections. These have almost invariably indicated a reduction in resistance to infections with increased morbidity and mortality from the short-term and long-term use of hormones.[2] This has often been expressed in such a manner as to permit an interpretation of "dangers ahead" for all patients with infections who are recipients of the adrenocortical hormones.

The subject has recently been reviewed by Thomas,[3] who, during the past few years, has carried out some brilliant experiments in animals aimed at uncovering some of the mechanisms involved. His concluding remarks regarding the available clinical data are most pertinent:

> . . . The vast majority of clinical reports dealing with ACTH and cortisone have concentrated on the successes of the agents in the face of great odds, and therefore deal to a large extent with the happy endings. Now, at the end of five years or so of experience, we have little information about the possible damaging effects of treatment, except for artificial situations involving experimental animals and occasional instances of fatal septicemia or vascular thrombosis in human beings. This may mean either that the human situation is an extremely fortunate one, with mostly good reactions and few bad ones, or that we have been concentrating our attention too closely on the bright side of things. We are in need, at this stage of events, of a more objective collection of information. As an example, it has been reported that some of the manifestations of periarteritis nodosa and lupus erythematosus occur in patients with rheumatoid arthritis after the cessation of treatment with large doses of cortisone. I have recently seen two patients in whom cortisone was administered for what appeared to be minor degrees of chronic rheumatoid arthritis of long standing; both developed the classical picture of periarteritis nodosa within less than a month and died. Two other patients developed unrecognized disseminated sepsis during treatment with cortisone and subsequently died, and at autopsy both showed glomerular thrombosis and tubular necrosis similar to the lesions which we have encountered in the kidneys of cortisone-treated rabbits following endotoxin. It is difficult to interpret isolated, fragmentary observations such as these. It is conceivable that they are based on chance, or that they simply represent instances in which cortisone has had no effect on the progress of disease. But the alternative explanation, which is that cortisone may actually cause an enhancement of tissue damage or may allow new kinds of damage to

occur, does deserve some consideration. A central clearing-house for such material, which would review not only the evident untoward results of treatment, but also the instances of apparent failure of treatment, would be a valuable institution for the next five years' experience with hormone therapy.

To these remarks may be added the hope and expectation that some experienced observers, with proper facilities for adequate studies, in institutions with sufficient clinical material will so control their studies in all patients that the results can be properly interpreted; only in this manner will the true value of these agents be finally assessed.

Meanwhile, the physician confronted with patients must make decisions on the basis of the facts that are presented and on whatever reliance he can place on the interpretations of those presenting the facts. Under such conditions, even the most skeptical and critical scientist among physicians must often compromise with his own best judgment when presented with the experiences and interpretations of others in an area in which he himself has limited competence or experience, or when, in his own field, the experiences and interpretations of others differ from his own. Such compromises are sometimes necessary to avoid criticism and are made in all fairness to the patient, until more convincing evidence is brought forth that permits a more decisive stand.

Regarding the use of hormones in infections, Thomas,[1] in the role of both scientist and physician, summed up his practical approach to the problem as follows:

> It is difficult to be sanguine about drugs with such side-effects as these, and it is not enough to say that some of the reactions are transitory or reversible, or that they do not occur very often. If these can be the immediate effects, we should await the much later effects of treatment, especially prolonged treatment, with meticulous attention, and I submit with some anxiety. And in the meanwhile, until the data of a decade or longer have been reviewed with care, the clinical use of these hormones should not be extended beyond the areas in which it can be predicted that they may save or prolong life, or relieve intractable suffering. This is especially to be emphasized, I believe, for the infectious diseases, in which something of a vogue for the use of cortisone and ACTH as "adjuncts" of therapy is discernible on the horizon.

These remarks certainly do not bespeak conviction that ACTH or cortisone is ever really life saving in the treatment of severe infections as such; nor do they relieve the uneasy feeling that these hormones may not be devoid of harm in such situations.

References

1. Kinsell, L. W., and Jahn, J. P. Combined hormonal-antibiotic therapy in patients with fulminating infections. *Arch. Int. Med.* **96**: 418-427, 1955.
2. Kass, E. H., and Finland, M. Adrenocortical hormones in infection and immunity. *Ann. Rev. Microbiol.* **7**:361-388, 1953.
3. Thomas, L. Cortisone, ACTH and infection. *Bull. New York Acad. Med.* **31**:488-499, 1955.

MEDICAL JOURNALISTS CONFER

THE value to American medical practice of the state medical journals, the quality of their content and the sincerity and ability of their editors was brought out more clearly than ever before at the biennial gathering of editors and business managers in Chicago in November. Like its predecessors, the two-day meeting was held under the auspices of the State Journal Advertising Bureau of the American Medical Association, a cohesive force that has helped to maintain a respected standard of journalism among the state-society-owned periodicals, whether or not they subscribe to its pecuniary services.

These services themselves, relating to the procurement of advertising material for the journals, have shown a steadily increasing annual return. This not only reflects the excellence of the Bureau management but emphasizes the cordial relations that it has helped to maintain between its thirty-three subscribing journals and the commercial interests that purchase their facilities.

One of the important points brought out early in the course of the meeting was the changed character of the monitoring practices controlling the selection of advertising material by the Bureau. As previously announced in these columns, Council acceptance as a requirement for inclusion is a thing of the past. Acceptance of a product now depends on an opinion handed down by the director of the Division of Therapy and Research of the American Medical Association, who is also chairman of its Advertising Committee, and on the whole a spirit of greater freedom in this regard prevails. The Bureau and its phalanx of journals have not yet "felt the weight of too much liberty," but the general character of medical advertising as it exists today, compared with only a few years ago, shows the change that has been coming about. The danger may even exist that this excess of friendliness between commercial and professional interests can some day become an embarrassment to the latter and less opulent of the two.

One innovation at this year's conference has been the revival of the intimate round-table discussion, operating in this ultramodern era under the somewhat less appropriate term of "workshop." Four such workshops comprised the activities of the first afternoon — on format and makeup, editing, publishing costs, and advertising. This method of examination and discussion of a subject again proved its value.

The question of the type of material to publish in a state medical journal remained, happily, specifically unanswered. If any conclusions should be reached on this subject they would be that much depends on the type of area and of practitioner that the journal must serve. A journal designed to fill the needs of

the practitioners of a thinly settled agricultural region may well differ in its content from the journal that is read largely in a teeming industrial area. None of them, however, written and edited as they are by and for the members of one of the learned professions, need be of inferior scientific or literary quality.

Certain words of Paul to the Corinthians might be adopted as a standard motto: "Seeing then that we have such hope, we use great plainness of speech."

NEWSLETTER

NEARLY synchronous in date of appearance with this issue of the *Journal,* — which ushers in the 144th year since the *New England Journal of Medicine and Surgery* first appeared on the doorsteps of its subscribers and introduces Volume 254 of the series that started in 1828 with the publication of the *Boston Medical and Surgical Journal,* — the first of their Newsletters will be mailed to the fellows of the Massachusetts Medical Society.

The Newsletter, series of 1956, is planned to appear at approximately two-month intervals, but its producers refuse to be bound by any such pedestrian schedule. If news is plentiful an extra edition may be slipped in. Published and distributed for the Society by the *Journal* it will emanate from the office of the Secretary at 22 The Fenway. It will be edited by Mr. Everett R. Spencer, Jr., of the Society's office of Education and Information, and his and the Secretary's skilled hands will be discerned in its present character and future development.

One of the Editors of this Journal has recently been using the bromide of potassium in spermatorrhoea, with happy effects.—Cincinnati Med. Observer.

Boston M. & S. J., *Jan. 10, 1855*

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Das Gesundheitswesen in der Bundesrepublik Deutschland. Adapted by Min.-Rat Dr. Med. Freidrich Koch and Oberreg.-und Med.-Rätin Dr. Med. Maria Daelen. 8°, paper, 100 pp., with 28 illustrations. Stuttgart: Georg Thieme, 1954. DM 6. *(Schriftenreihe aus dem Gebiete des Öffentlichen Gesundheitswesens; Herausgegeben von der Abteilung Gesundheitswesen des Bundesministeriums des Innern, Heft 1.)*

The authors describe the health measures carried out in the German Republic. They present a summary of organization and administration, medical personnel, general hygiene and control of infectious diseases, assistance for various types of disease and social medicine, including insurance.

Liver Injury. Transactions of the Twelfth Conference, September 21, 22 and 23, 1953, Princeton, N. J. Edited by F. W. Hoffbauer, M.D., associate professor, Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minnesota. 8°, cloth, 231 pp., with 52 illustrations. New York: Josiah Macy, Jr., Foundation, 1954. $4.25.

The subjects discussed at this conference included liver and carbohydrate and fat metabolism, cardiovascular lesions in choline-deficient rats, and liver protein metabolism.

Administrative Medicine: Transactions of the Second Conference December 8, 9, and 10, 1953, Princeton, N. J. Edited by George S. Stevenson, M.D., national and international consultant, National Association for Mental Health. New York: Josiah Macy, Jr., Foundation, 1954. $3.00.

The topics considered at this second conference included major components of administrative medicine, home-care programs, the health services of the Department of Health of Scotland and home-care studies.

Laboratory Techniques in Rabies. By D. d'Antona and others. 8°, cloth, 150 pp., with illustrations. Geneva: World Health Organization, 1954. $4.00.

This small monograph is the joint work of 14 contributors. The text is divided into five parts: diagnosis; methods of vaccine production; vaccine potency tests; production of hyperimmune serum; and laboratory animals.

Diseases Transmitted from Animals to Man. By Thomas G. Hull, Ph.D., secretary, Council on Scientific Assembly, and director, Bureau of Exhibits, American Medical Association. Fourth edition. 8°, cloth, 717 pp., with 67 tables and 104 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $12.50.

This standard reference book, first published in 1930, is the joint work of 25 distinguished contributors. The text has been thoroughly revised. Seven new chapters have been included in this new edition. Lists of references are appended to the chapters; the publishing is excellent. The book is recommended for all medical libraries and all interested persons.

Doctor to the Islands. By Tom and Lydia Davis. 8°, cloth, 331 pp., with illustrations. Boston: Little, Brown and Company, 1954. $4.50.

This narrative tells the true story of a Polynesian physician and his wife who spent six years in the Cook Islands. The book should be in all medical-history collections.

Childbirth: Theory and practical training. By Marjorie F. Chappell, D.N. (Lond.), S.R.N., C.S.P., S.C.M., H. V. Cert., health visitor, London City Council. With a foreword by C. Keith Vartan, F.R.C.S., F.R.G.O.G., obstetrician to the British Hospital for Mothers and Babies. 12°, cloth, 128 pp., with 35 illustrations. London: E. and S. Livingstone, Ltd., 1954. $2.50. (Distributed by Williams and Wilkins, Baltimore.)

Local Anesthesia: Brachial plexus. By R. R. Macintosh, M.A., D.M., F.R.C.S., F.F.A.R.C.S., D.A., M.D. (hon. causa), Buenos Aires and Aix-Marseilles, and Nuffield Professor of Anaesthetics, University of Oxford; and William W. Mushin, M.A., M.B., B.S. (Lond.), M.R.C.S., F.F.A. R.C.S., D.A., professor of anesthetics, Welch National School of Medicine, University of Wales. Illustrated by Miss M. McLarty. Third edition. 12°, cloth, 62 pp., with 32 illustrations. London: E. and S. Livingstone, Ltd., 1954. $3.00. (Distributed by Williams and Wilkins, Baltimore.)

The Diseases of Occupations. By Donald Hunter, M.D., F.R.C.P., physician, London Hospital. 8°, cloth, 1046 pp., with 435 illustrations. Boston: Little, Brown and Company, 1955. $20.00.

NOTICES

BOSTON COMMITTEE ON ALCOHOLISM

The seventh annual conference on alcoholism, under the auspices of the Boston Committee on Alcoholism, will be held at the John Hancock Hall, 200 Berkeley Street, on Wednesday, January 25. The conference theme and the title of the feature address given by Dr. Selden D. Bacon will be "1956 Concepts of Alcoholism." The afternoon session will start at 1 o'clock, and the evening session will follow dinner scheduled for 7 o'clock.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, Boston, on Tuesday, February 14, at 8 p.m.

The program, Dr. James H. Means presiding, is as follows:

Some Observations on the Action of Thyroxine on Oxidative Enzymes in Vitro. Edith C. Wolff and Eric G. Ball, Harvard Medical School.

Qualitative Differences in the Plasma Thyroid Hormone Complex in Disease. Milton W. Hamolsky and A. Stone Freedberg, Beth Israel Hospital and Harvard Medical School.

Studies of Peripheral Degradation of Thyroxine in Graves's Disease and Other Thyroidal Disorders. Sidney Ingbar and Norbert Freinkel, Boston City Hospital and Harvard Medical School.

Estimation of Peripheral Iodide Release. Belton Burrows, Boston Veterans Administration Hospital and Boston University School of Medicine.

Normal and Abnormal Metabolism of Iodotyrosine. John B. Stanbury, A. A. H. Kassanaar, I. W. A. Meijers and Andries Querido, Massachusetts General Hospital, Harvard Medical School and Academisch Ziekenhuis, Leiden, Holland.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 5–26. Consultation Clinics for Crippled Children in Massachusetts. Page 1177, issue of December 29.

JANUARY 9. New England Cardiovascular Society. Page 1135, issue of December 22.

JANUARY 9–14. Pan American Congress of Ophthalmology. Page 944, issue of November 24.

JANUARY 10. Harvard Medical Society. Page 1135, issue of December 22.

JANUARY 10. Massachusetts Institute of Technology Symposium. Page 1180, issue of December 29.

JANUARY 10. Soldiers' Home Staff Meeting. Page 1180, issue of December 29.

JANUARY 13, 20 and 27 and FEBRUARY 3. Yale University School of Medicine. Yale-New Haven Medical Center. Page 1092, issue of December 15.

JANUARY 16. Hartford Medical Society. Page 708, issue of October 20.

JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2. Fried Lecture Series. Page 535, issue of September 22.

JANUARY 20–27. Fifth Panamerican Congress of Gastroenterology. Page 946, issue of October 27.

JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25. Massachusetts Heart Association. Page 623, issue of October 16.

JANUARY 25, MARCH 21 and APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

JANUARY 25. Boston Committee on Alcoholism. Notice above.

JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

FEBRUARY 13–16. American College of Surgeons. Page 1136, issue of December 22.

FEBRUARY 14. Harvard Medical Society. Notice above.

FEBRUARY 15, MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 206, issue of August 4.

FEBRUARY 20–22. Atlanta Graduate Medical Assembly. Page 1136, issue of December 22.

MARCH 19–22. American Academy of General Practice. Page 1092, issue of December 15.

MARCH 24 and 25. American Psychosomatic Society. Page 260, issue of August 11.

MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.

MAY 3–5. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.

JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.

JUNE 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.

AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.

SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JANUARY 12

THURSDAY, JANUARY 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m. Thoracic Conference. The Thoracic Service Presents Cases of Medical and Surgical Interest. Drs. Dwight E. Harken and Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, JANUARY 13

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference, X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, JANUARY 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten, Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, and J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JANUARY 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xxii)